Synthesis D. V. Osipov et al. Paper

Reactions of *o*-Quinone Methides with Halogenated 1*H*-Azoles: Access to Benzo[*e*]azolo[1,3]oxazines

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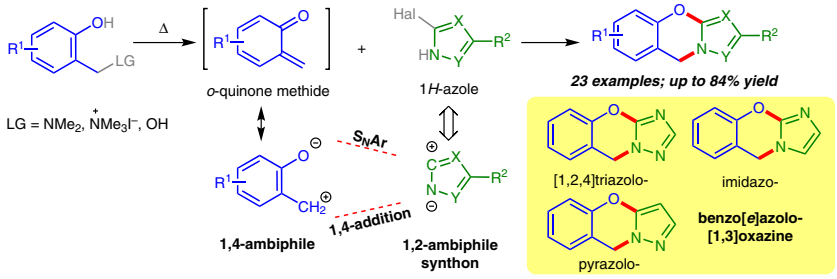

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Abstract A simple route to the series of azolo-condensed benzo[*e*][1,3]oxazines such as 9*H*-benzo[*e*][1,2,4]triazolo[5,1-*b*][1,3]oxazines, 9*H*-benzo[*e*]pyrazolo[5,1-*b*][1,3]oxazines, and 5*H*-benzo[*e*]imidazo[2,1-*b*][1,3]oxazines has been developed. The reaction proceeds through formation of an *ortho*-quinone methide intermediate followed by aza-Michael addition of the halogenoazoles to the *o*-quinone methide and intramolecular nucleophilic substitution.

Key words quinone methide, 1*H*-azoles, cascade reactions, aza-Michael reaction, benzo[*e*]azolo[1,3]oxazines

Condensed systems based on 1*H*-azoles attached with another heterocycle at the C–N bond are attracting the high attention of researchers. The principal reason for this interest is the high biological activity of some heteroannulated 1*H*-azoles such as [1,5]-fused 1,2,4-triazoles and pyrazoles, as well as [1,2]-fused imidazoles (Figure 1). Among the biologically relevant 1,2,4-triazoles, there are cytokine TNF-α and IL-6 inhibitors,[1] the ligands of benzodiazepine receptors,[2] modulators of γ-secretase,[3] compounds effective against hepatitis B virus,[4] and compounds exhibiting anticonvulsant[5] and antihypertensive activities.[6] One of the most attractive classes of antituberculosis compounds is [1,2]-annulated imidazoles, such as (6*S*)-2-nitro-6-{[4-(trifluoromethoxy)benzyl]oxy}-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazine (Pretomanid, PA-824) and its analogues.[7] Furthermore, imidazo[2,1-*b*][1,3,4]thiadiazoles exhibit anticancer[8] and antihyperlipidemic activity.[9] Some of the heteroannulated pyrazoles possess antitubercular,[10] anti-inflammatory[11] and other types of activities.[12]

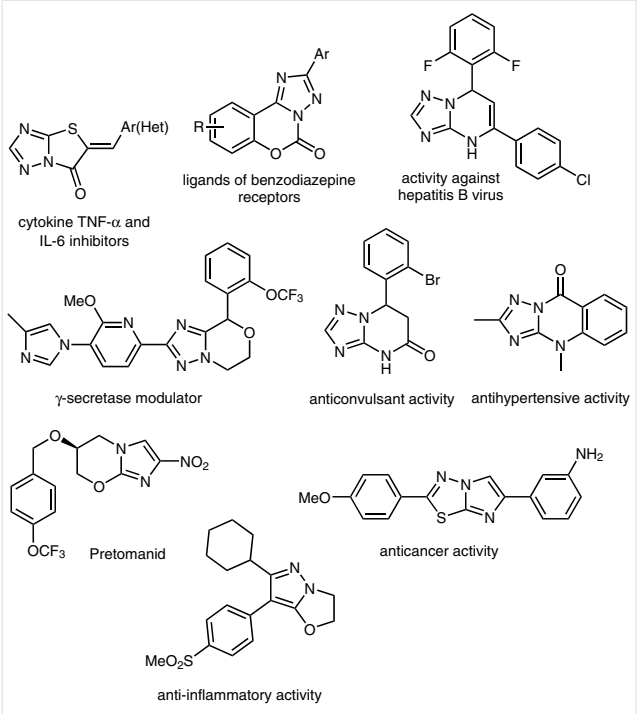


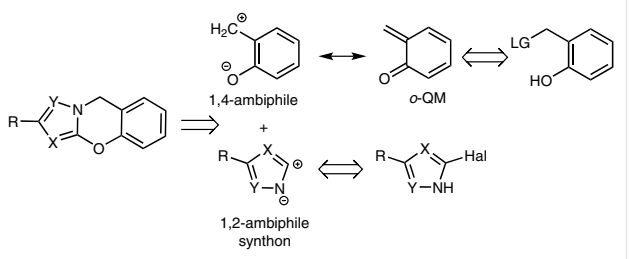
Figure 1 Selected examples of biologically active condensed 1*H*-azoles

On the other hand, there is an ongoing need to establish new synthetic methodologies for the construction of different heterocycles, which are important for the development of the theoretical chemistry of heterocycles and for drug discovery.[13] The most preferable tools towards the achievement of this goal seem to be cascade (or domino) reactions due to the benefits of their use.[14]

The cascade aza-Michael intramolecular nucleophilic substitution or addition reactions seem to be a useful sequence to produce nitrogen-containing heterocycles with

high step economy. *o*-Quinone methides (*o*-QMs) can be efficiently used in these reactions as Michael acceptors.[15] At the same time, in spite of numerous reports on aza-Michael reactions of *o*-QMs in biological systems,[16] they are seldom used for the construction of heterocycles.

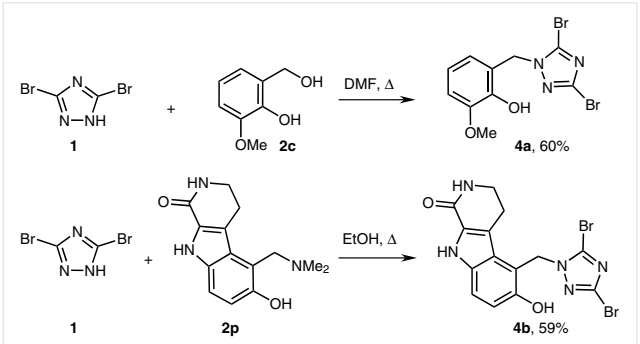
As part of our current studies on the development of new routes to heterocyclic systems from *o*-QMs,[15e–j,17] we focused our attention on the reaction of *o*-QMs with halogen-1*H*-azoles. In the case of presence of good leaving group such as halogen, near nucleophilic nitrogen atom azoles may be considered as 1,2-ambiphiles.[18] Reactions of this type of azoles with *o*-QMs as 1,4-ambiphiles[15d,17a–c] lead to different benzo[*e*]azolo[1,3]oxazines (Scheme 1).



Scheme 1 Retrosynthetic analysis of benzo[*e*]azolo[1,3]oxazine unit

It was found that condensation of 3,5-dibromo-1,2,4-triazole (**1**) with a series of *o*-QM precursors **2** by heating equimolar quantities of the starting materials in DMF in the presence of K_2CO_3 gave benzo[*e*][1,2,4]triazolo[5,1-*b*][1,3]oxazines **3** in good yields (Table 1). *o*-QMs were generated from *o*-hydroxybenzyl alcohols **2a–c**, Mannich base **2d**, and quaternary ammonium salts **2e–l**,**n** derived from phenols. The reactions were performed in DMF under reflux for completely thermal decomposition of the *o*-QM precursors. Products can be easily purified from impurities by single recrystallization, chromatographic purification is not usually required. The reaction was performed with comparable yields on several different scales (up to 20 mmol). It should be noted that none of the products of the *o*-QM oligomerization, which are obtained in the usual pyrolytic methods[19] were detected. In the case of esters **2i** and **2n** low yields of the products **3i** (24%) and **3n** (39%) were caused by partial hydrolysis of the ester group (Table 1, entries 9,14). The sterically hindered triazolobenzoxazines **3a**,**k**,**l** were obtained in good yields, indicating that steric hindrance had no obvious influence on the efficiency of this method (entries 1,11,12). We could not obtain product **3m** from the methiodide of 2-[(dimethylamino)methyl]-4-nitrophenol. Nevertheless, in the reaction with more reactive precursor of *o*-QM **2m**, the corresponding triazolobenzoxazine **3m** was obtained in 64% yield (entry 13). In order to broaden the scope of the present method, this protocol was attempted using bis-Mannich base **2o** derived from hydroquinone. As a result, novel heterocyclic system **3o** was prepared in 72% yield (entry 15). Besides, 3-chloro-1,2,4-triazole can be also involved in this reaction instead of 3,5-dibromo-1,2,4-triazole (**1**) (entry 16).

In the absence of a base, the reaction can be stopped at the stage of 2-(1*H*-1,2,4-triazol-1-ylmethyl)phenols **4a**,**b** (Scheme 2). It is interesting to note that the generation of *o*-QM from Mannich base **2p** took place at milder conditions (in ethanol under reflux), which can be explained by increased conjugation in this intermediate.



Scheme 2 Synthesis of 2-(1*H*-1,2,4-triazol-1-ylmethyl)phenols **4a**,**b**. *Reagents and conditions*: **1** (2.9 mmol) and *o*-QM precursor **2** (2.9 mmol) were refluxed in DMF (10 mL, for **2c**) or EtOH (10 mL, for **2p**) for 2 h.

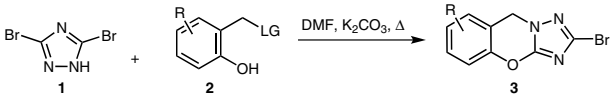
The mechanism of the reaction is believed to involve the formation of the *o*-QM intermediate **A**, which is generated in situ from the corresponding precursor **2**. Subsequent aza-Michael addition of the *o*-QM with **1** and intramolecular nucleophilic substitution via formation of the Meisenheimer-type complex **B** affords the expected benzo[*e*][1,2,4]triazolo[5,1-*b*][1,3]oxazines **3** (Scheme 3). The driving force of the reaction is the resulting rearomatization of the benzene ring and the entropy factor, favoring intramolecular versus intermolecular nucleophilic addition-elimination reactions in the 1,2,4-triazole moiety. During the reaction only a small concentration of *o*-QM is produced, which prevents its oligomerization and leds to good yields of the products of *N*-hydroxybenzylation. K_2CO_3 is required to facilitate the *o*-QM generation and subsequent cyclization to the benzo[*e*][1,2,4]triazolo[5,1-*b*][1,3]oxazine ring system. It should be noted that the alkylation of 3,5-dibromo-1,2,4-triazole (**1**) with *o*-QM precursors may give rise to two isomeric triazolobenzoxazines **3** and **5**. However, in all cases, the alkylation occurs at $N^{1(2)}$ rather than N^4, reflecting the higher nucleophilicity of N–N systems (α-effect).[20]

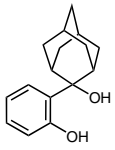
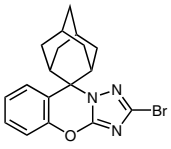
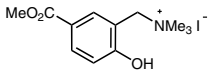
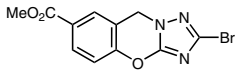
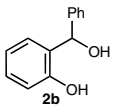
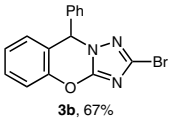
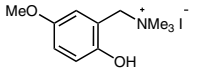
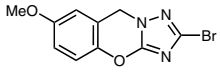
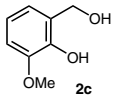
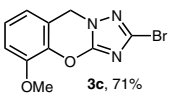
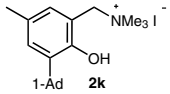
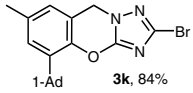
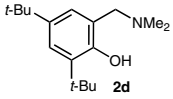
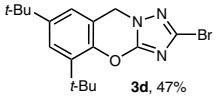
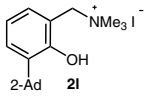
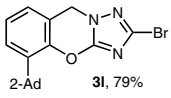
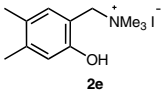
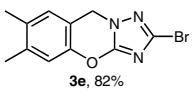
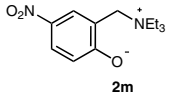
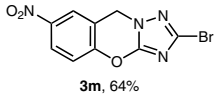
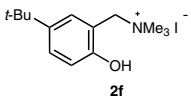
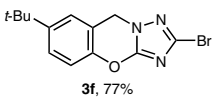
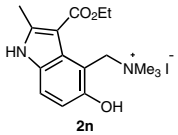
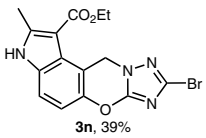
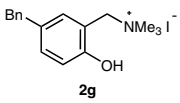
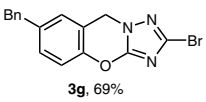
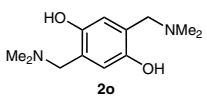
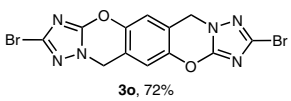
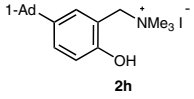
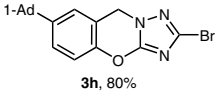
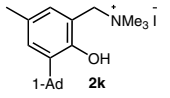
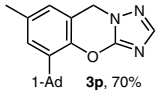
The generation of the *o*-QM under reaction conditions from Mannich base **2d** was indirectly confirmed by its trapping with *N*-vinyl-2-pyrrolidone with formation of the corresponding Diels–Alder cycloadduct **6** in 72% yield (Scheme 4). However, a stepwise reaction route without formation of

o-QM intermediate via nucleophilic substitution of leaving group by triazole moiety and ring closure could not be completely rejected.

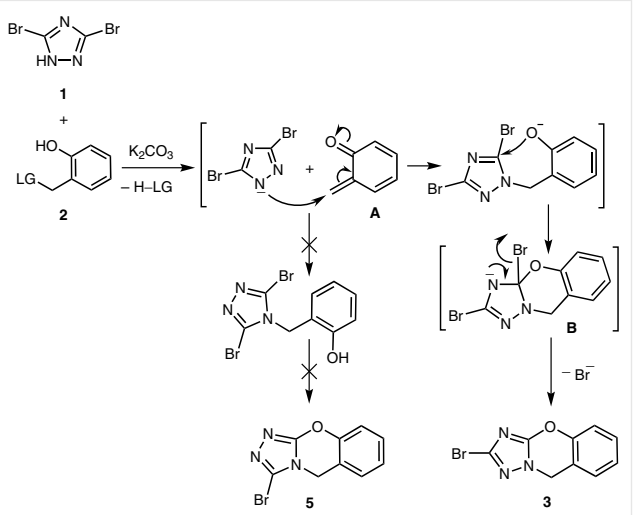
The reaction of **1** and 4-chloro-2,6-bis(hydroxymethyl)phenol (**2q**) due to the tandem generation of the *o*-QM gives benzoxazine **3q** containing two 1,2,4-triazole moieties (Scheme 5). The reaction is a domino-process that in-

Table 1 Scope and Yields of the Synthesis of Compounds **3**[a]

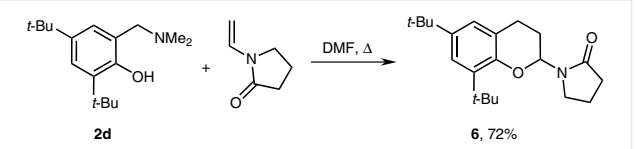


Entry	*o*-QM precursor	Product	Entry	*o*-QM precursor	Product
1	 **2a**	 **3a**, 61%	9	 **2i**	 **3i**, 24%
2	 **2b**	 **3b**, 67%	10	 **2j**	 **3j**, 72%
3	 **2c**	 **3c**, 71%	11	 **2k**	 **3k**, 84%
4	 **2d**	 **3d**, 47%	12	 **2l**	 **3l**, 79%
5	 **2e**	 **3e**, 82%	13[b]	 **2m**	 **3m**, 64%
6	 **2f**	 **3f**, 77%	14	 **2n**	 **3n**, 39%
7	 **2g**	 **3g**, 69%	15[c]	 **2o**	 **3o**, 72%
8	 **2h**	 **3h**, 80%	16[d]	 **2k**	 **3p**, 70%

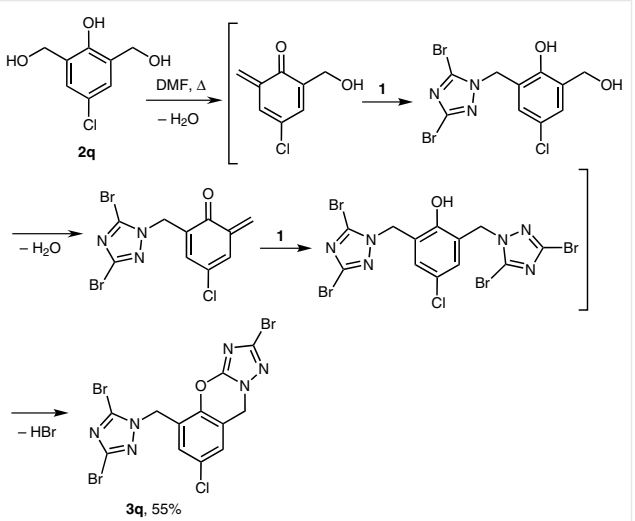
[a] Reaction conditions: **1** (2.9 mmol), *o*-QM precursor **2** (2.9 mmol), and K_2CO_3 (8.7 mmol) were refluxed in DMF (10 mL) for 4 h.
[b] Reaction was carried out in mixture of MeCN and H_2O (2:1) at 80 °C without K_2CO_3.
[c] Two equivalents of 3,5-dibromo-1,2,4-triazole (**1**) were used.
[d] 3-Chloro-1,2,4-triazole was used instead of 3,5-dibromo-1,2,4-triazole (**1**).



Scheme 3 Proposed mechanism for the formation of benzo[*e*][1,2,4]triazolo[5,1-*b*][1,3]oxazines **3**



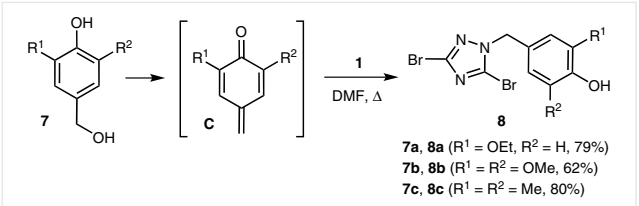
Scheme 4 Trapping of *o*-quinone methide generated from Mannich base **2d**. *Reagents and conditions*: *N*-Vinyl-2-pyrrolidone (4.3 mmol) and *o*-QM precursor **2d** (3.8 mmol) were refluxed in DMF (10 mL) for 12 h.



Scheme 5 Synthesis of compound **3q**. *Reagents and conditions*: **1** (5 mmol) and *o*-QM precursor **2q** (2.5 mmol) were refluxed in DMF (10 mL) for 5 h.

cludes five steps: two dehydration reactions, two Michael-type additions, and one nucleophilic substitution reaction. It was difficult to stop the reaction at the stage of the formation of the corresponding 1,2,4-triazol-1-ylmethylphenol even in the absence of a base. The formation of the product **3q** indicates a greater rate of 1,4-addition rather than intramolecular nucleophilic substitution.

Magnetic nonequivalence of the 1,2,4-triazole carbon atoms in the compounds **4a**,**b** and also **3q** (8 signals for **4a** and 10 signals both for **4b** and **3q** in the aromatic region of ^{13}C NMR spectra) indicates that the alkylation occurred at the $N^{1(2)}$ atom of the 1,2,4-triazole ring rather than N^4. The same regioselectivity was observed in reactions of **1** with *p*-hydroxybenzyl alcohols **7** as precursors of *p*-quinone methides **C**, which allow to prepare the 4-[(1,2,4-triazol-1-yl)methyl]phenols **8a–c** in good yields (Scheme 6).



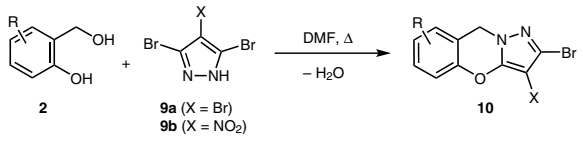
Scheme 6 Reactions of *p*-hydroxybenzyl alcohols with 3,5-dibromo-1,2,4-triazole **1**. *Reagents and conditions*: **1** (2.9 mmol) and *p*-QM precursor **7** (2.9 mmol) were refluxed in DMF (10 mL) for 4 h.

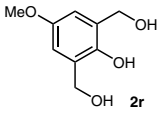
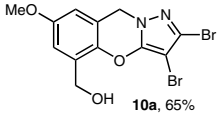
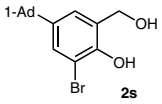
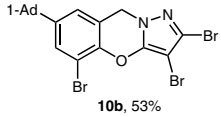
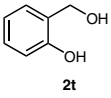
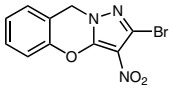
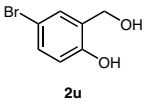
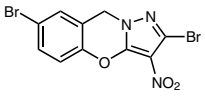
We have also applied the developed method to the synthesis of 9*H*-benzo[*e*]pyrazolo[5,1-*b*][1,3]oxazines **10a–d** from salicylic alcohols **2r–u** and 3,4,5-tribromopyrazole (**9a**) and 3,5-dibromo-4-nitropyrazole (**9b**) (Table 2). In the case of **9b**, the presence of a base is not required because the nitro group in the pyrazole moiety significantly increases the reactivity to nucleophilic substitution and the ability of the bromine atoms to be eliminated.

The reaction of ammoniomethylphenolate **2m** and 2-bromo-1*H*-imidazole-4,5-dicarbonitrile (**11a**) or dimethyl 2-bromo-1*H*-imidazole-4,5-dicarboxylate (**11b**) in aqueous acetonitrile leads to 5*H*-benzo[*e*]imidazo[2,1-*b*][1,3]oxazines **12a**,**b** in 47% and 57% yield, respectively (Scheme 7). At the same time, reactions of salicylic alcohols with 2-bromo-, 2-chloro-, 2-(methylthio)-1*H*-benzo[*d*]imidazoles or 2-bromo-4,5-diphenyl-1*H*-imidazole require harsh conditions both for efficient generation of *o*-QM intermediates and for successful further cyclization.[15i,j] It should be noted that the reaction of the imidazoles **11a**,**b** with other precursors of the *o*-QMs (salicylic alcohols, phenolic Mannich bases, quaternary salts) in refluxing aqueous acetonitrile did not proceed, and in boiling DMF a complex mixture of unidentified products was obtained.

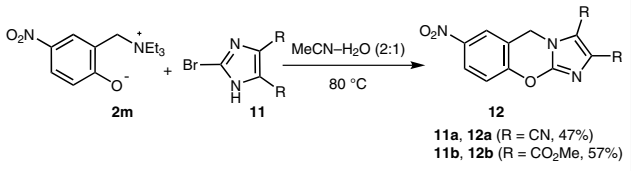
The IR spectra of compounds **3a–q**, **10b–d**, and **12a**,**b** show the absence of stretching vibration bands for an O–H bond, which supports the cyclic structure of the compounds obtained. The methylene signals in ^1H NMR spectra shift downfield due to the electron-withdrawing azole group and appear as singlets in the region of 5.21–5.64

Table 2 Scope of the Benzo[*e*]pyrazolo[5,1-*b*][1,3]oxazine Formation



Entry	*o*-QM precursor	Product
1[a]	 **2r**	 **10a**, 65%
2[a]	 **2s**	 **10b**, 53%
3[b]	 **2t**	 **10c**, 80%
4[b]	 **2u**	 **10d**, 75%

[a] Reaction conditions: **9a** (2.5 mmol), *o*-QM precursor **2r** or **2s** (2.5 mmol), and K_2CO_3 (7.5 mmol) were refluxed in DMF (10 mL) for 5 h.
[b] Reaction conditions: **9b** (2.5 mmol) and *o*-QM precursor **2t** or **2u** (2.5 mmol) were refluxed in DMF (10 mL) for 5 h.



Scheme 7 Synthesis of benzo[*e*]imidazo[2,1-*b*][1,3]oxazines **12**. *Reagents and conditions*: **11a** or **11b** (1.2 mmol) and *o*-QM precursor **2m** (1.2 mmol) were refluxed in H_2O (1.5 mL) and MeCN (3 mL) for 4 h.

ppm. In the ^{13}C NMR spectra, the signals of the methylene carbon atoms appear at 44.6–47.0 ppm. The IR spectra of compounds **4a**,**b** show a broad absorption band in the range 3400–3200 cm^{-1} corresponding to the stretching vibration of a hydroxyl group associated with hydrogen bonding and singlets at δ = 9.10 and 9.21 in the ^1H NMR spectra were assigned to OH protons. In the case of compounds **8a–c**, absorption of the phenolic hydroxyl groups was observed as strongly broadened diffuse bands with several maxima in the region of 3000–3500 cm^{-1}. The number of protons that were directly linked to ^{13}C atoms, inferred from DEPT spectra, was in accordance with the presented structures.

In conclusion, a useful method for the synthesis of 9*H*-benzo[*e*][1,2,4]triazolo[5,1-*b*][1,3]oxazines, 9*H*-benzo[*e*]pyrazolo[5,1-*b*][1,3]oxazines, and 5*H*-benzo[*e*]imidazo[2,1-*b*][1,3]oxazines based on cascade aza-Michael and intramolecular nucleophilic substitution reactions was developed. Their synthesis by the suggested procedure does not require an excess of any reagents, includes the use of available reagents, simple workup procedure, scalability, and good functional group tolerance. The Michael-type addition reaction of *o*-QMs and azoles is advantageous due to its higher regioselectivity compared to alkylation reactions using alkyl halides or alkyl sulfates. Besides, due to the presence of the bromine atoms some of the prepared products may be valuable intermediates for obtaining aryl-substituted azolobenzoxazines by C–C cross-coupling methods.[21]

Melting points were determined by capillary method on a SRS OptiMelt MPA100 apparatus and are uncorrected. FTIR-spectra were taken on a Shimadzu FTIR-8400S spectrophotometer as KBr pellets. ^1H and ^{13}C NMR spectra (including DEPT-135 experiments) were recorded on a Jeol JNM-ECX 400 spectrometer (400 and 100 MHz, respectively) in DMSO-d_6 or $CDCl_3$ solutions, relative to residual solvent signal [$CHCl_3$ δ = 7.26 ppm (^1H), $CDCl_3$ δ = 77.0 ppm (^{13}C); DMSO-d_6 δ = 2.50 ppm (^1H), δ = 39.5 ppm (^{13}C)]. Chemical shifts and coupling constants were recorded in units of parts per million and hertz, respectively. Mass spectra were recorded on a Finnigan Trace DSQ chromato mass spectrometer with direct introduction of the sample into the ion source (EI, 70 eV, mass-selective detector). Elemental analyses were carried out on a Euro Vector EA-3000 automatic CHNS analyzer.

The reported *o*-QM precursors were prepared according to literature procedures.[17d–f,22] 4-Nitro-2-[(triethylammonio)methyl]phenolate (**2m**) was prepared from 2-(chloromethyl)-4-nitrophenol and triethylamine.[22e]

Benzo[*e*][1,2,4]triazolo[5,1-*b*][1,3]oxazines 3; General Procedure

3,5-Dibromo-1,2,4-triazole (**1**; 658 mg, 2.9 mmol) or 3-chloro-1,2,4-triazole (300 mg, 2.9 mmol), *o*-quinone methide precursor **2** (2.9 mmol), and K_2CO_3 (1.2 g, 8.7 mmol) were refluxed for 4 h in DMF (10 mL). After completion of the reaction, the mixture was cooled, and poured into H_2O (30 mL). The precipitate formed was collected by filtration, washed with H_2O, dried, and recrystallized.

2′-Bromospiro[adamantane-2,9′-benzo[*e*][1,2,4]triazolo[5,1-*b*][1,3]oxazine] (3a)

Yield: 658 mg (61%); colorless crystals; mp 214–216 °C (DMF).

IR (KBr): 2978, 2916, 2884, 1524, 1489, 1466, 1447, 1269, 1219, 1188, 1177, 1095, 1038, 972, 825, 748 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.90 (d, *J* = 7.8 Hz, 1 H, Ar), 7.42–7.49 (m, 2 H, Ar), 7.32–7.36 (m, 1 H, Ar), 2.49–2.54 (m, 4 H, Ad), 2.01–2.05 (m, 2 H, Ad), 1.80–1.87 (m, 4 H, Ad), 1.64–1.69 (m, 4 H, Ad).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 157.0 (C), 152.2 (C), 135.5 (C), 130.0 (CH), 129.6 (C), 127.9 (CH), 126.0 (CH), 118.5 (CH), 69.2 (C-2, Ad), 37.9 (CH_2, Ad), 35.1 (2 × CH, Ad), 35.0 (2 × CH_2, Ad), 33.4 (2 × CH_2, Ad), 26.7 (CH, Ad), 26.5 (CH, Ad).

MS (EI): *m*/*z* (%) = 371 (24, $[M]^+$), 354 (5, $[M - OH]^+$), 316 (7), 292 (90, $[M - Br]^+$), 250 (13), 226 (57, $[M - C_2BrN_3]^+$), 196 (32), 183 (37), 172 (37), 165 (60), 152 (62), 131 (57), 128 (49), 115 (78), 107 (52), 103 (42), 91 (98), 79 (83), 77 (100).

Anal. Calcd for $C_{18}H_{18}BrN_3O$: C, 58.08; H, 4.87; N, 11.29. Found: C, 58.14; H, 4.93; N, 11.24.

2-Bromo-9-phenyl-9*H*-benzo[*e*][1,2,4]triazolo[5,1-*b*][1,3]oxazine (3b)

Yield: 638 mg (67%); colorless crystals; mp 219–221 °C (EtOH).

IR (KBr): 1593, 1543, 1514, 1483, 1454, 1285, 1196, 1173, 1146, 1099, 988, 908, 833, 812, 756, 737, 694 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.35–7.40 (m, 4 H, Ar), 7.30 (d, *J* = 8.7 Hz, 1 H, Ar), 7.16–7.25 (m, 3 H, Ar), 7.06 (d, *J* = 7.8 Hz, 1 H, Ar), 6.41 (s, 1 H, H-9).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 153.6 (C), 147.3 (C), 139.0 (C), 138.7 (C), 130.1 (CH), 129.4 (CH), 129.3 (2 × CH), 128.7 (CH), 128.0 (2 × CH), 125.8 (CH), 119.1 (C), 117.6 (CH), 61.3 (CH).

Anal. Calcd for $C_{15}H_{10}BrN_3O$: C, 54.90; H, 3.07; N, 12.80. Found: C, 54.98; H, 3.07; N, 12.80.

2-Bromo-5-methoxy-9*H*-benzo[*e*][1,2,4]triazolo[5,1-*b*][1,3]oxazine (3c)

Yield: 581 mg (71%); colorless crystals; mp 240–242 °C (DMF).

IR (KBr): 2841, 1595, 1557, 1522, 1489, 1441, 1341, 1327, 1296, 1275, 1182, 1152, 1082, 953, 885, 785 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6 at 80 °C): δ = 7.19 (t, *J* = 8.0 Hz, 1 H, Ar), 7.08 (d, *J* = 8.0 Hz, 1 H, Ar), 6.89 (d, *J* = 7.6 Hz, 1 H, Ar), 5.28 (s, 2 H, CH_2), 3.86 (s, 3 H, CH_3O).

^{13}C NMR (100 MHz, DMSO-d_6 at 80 °C): δ = 154.0 (C), 148.3 (C), 137.8 (C), 137.2 (C), 126.1 (CH), 119.1 (CH), 117.0 (C), 113.1 (CH), 56.9 (CH_3O), 46.2 (CH_2).

Anal. Calcd for $C_{10}H_8BrN_3O_2$: C, 42.58; H, 2.86; N, 14.90. Found: C, 42.68; H, 2.77; N, 14.82.

2-Bromo-5,7-di-*tert*-butyl-9*H*-benzo[*e*][1,2,4]triazolo[5,1-*b*][1,3]oxazine (3d)

Yield: 497 mg (47%); colorless crystals; mp 145–146 °C (MeOH).

IR (KBr): 2967, 2905, 2870 (C–H *t*-C_4H_9), 1609, 1564, 1524, 1479, 1460, 1443, 1364, 1294, 1242, 1215, 1198, 1165, 1146, 1117, 986, 874, 800, 718 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 2.3 Hz, 1 H, Ar), 7.04 (d, *J* = 2.3 Hz, 1 H, Ar), 5.27 (s, 2 H, CH_2), 1.44 (s, 9 H, *t*-C_4H_9), 1.31 (s, 9 H, *t*-C_4H_9).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.7 (C), 148.2 (C), 144.6 (C), 138.4 (C), 138.3 (C), 124.7 (CH), 121.8 (CH), 113.9 (C), 46.5 (CH_2), 35.4 [*C*(CH_3)$_3$], 34.8 [*C*(CH_3)$_3$], 31.4 [C(*C*H_3)$_3$], 30.1 [C(*C*H_3)$_3$].

Anal. Calcd for $C_{17}H_{22}BrN_3O$: C, 56.05; H, 6.09; N, 11.54. Found: C, 56.11; H, 6.02; N, 11.61.

2-Bromo-6,7-dimethyl-9*H*-benzo[*e*][1,2,4]triazolo[5,1-*b*][1,3]oxazine (3e)

Yield: 666 mg (82%); colorless crystals; mp 240–241 °C (EtOH–DMF, 4:1).

IR (KBr): 2970, 2943, 2920, 2893, 2858, 1593, 1558, 1520, 1458, 1416, 1292, 1265, 1234, 1200, 1177, 1146, 1076, 1003, 987, 887, 717 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.11 (s, 1 H, Ar), 7.08 (s, 1 H, Ar), 5.21 (s, 2 H, CH_2), 2.21 (s, 3 H, CH_3), 2.18 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 154.1 (C), 145.7 (C), 138.5 (C), 137.1 (C), 134.1 (C), 128.4 (CH), 117.8 (CH), 112.7 (C), 45.9 (CH_2N), 19.6 (CH_3), 19.1 (CH_3).

Anal. Calcd for $C_{11}H_{10}BrN_3O$: C, 47.16; H, 3.60; N, 15.00. Found: C, 47.21; H, 3.62; N, 14.91.

2-Bromo-7-*tert*-butyl-9*H*-benzo[*e*][1,2,4]triazolo[5,1-*b*][1,3]oxazine (3f)

Yield: 688 mg (77%); colorless crystals; mp 146–148 °C (*i*-PrOH).

IR (KBr): 3055, 2962, 2905, 2870, 1597, 1558, 1520, 1504, 1423, 1366, 1288, 1219, 1204, 1184, 1157, 1122, 1099, 987, 876, 837, 798, 741, 717 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.41 (dd, *J* = 8.2, 2.3 Hz, 1 H, H-6), 7.39 (d, *J* = 2.3 Hz, 1 H, H-8), 7.20 (d, *J* = 8.2 Hz, 1 H, H-5), 5.28 (s, 2 H, CH_2), 1.26 (s, 9 H, *t*-C_4H_9).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 154.0 (C), 148.5 (C), 145.7 (C), 137.1 (C), 126.9 (CH), 124.8 (CH), 116.9 (CH), 115.4 (C), 46.4 (CH_2N), 34.8 [*C*(CH_3)$_3$], 31.6 [C(*C*H_3)$_3$].

Anal. Calcd for $C_{13}H_{14}BrN_3O$: C, 50.67; H, 4.58; N, 13.64. Found: C, 50.73; H, 4.64; N, 13.58.

2-Bromo-7-benzyl-9*H*-benzo[*e*][1,2,4]triazolo[5,1-*b*][1,3]oxazine (3g)

Yield: 685 mg (69%); colorless crystals; mp 185–186 °C (EtOH).

IR (KBr): 3024, 2905, 1601, 1562, 1520, 1497, 1462, 1431, 1404, 1288, 1258, 1200, 1150, 1111, 987, 895, 845, 764, 721, 694 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.13–7.28 (m, 8 H, Ar), 5.24 (s, 2 H, CH_2N), 3.91 (s, 2 H, C*H*$_2$Ph).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 153.9 (C), 146.2 (C), 141.3 (C), 139.2 (C), 137.1 (C), 130.2 (CH), 129.2 (2 × CH), 129.1 (2 × CH), 128.0 (CH), 126.7 (CH), 117.4 (CH), 116.0 (C), 46.2 (CH_2N), 40.7 (CH_2).

Anal. Calcd for $C_{16}H_{12}BrN_3O$: C, 56.16; H, 3.53; N, 12.28. Found: C, 56.22; H, 3.48; N, 12.33.

7-(Adamantan-1-yl)-2-bromo-9*H*-benzo[*e*][1,2,4]triazolo[5,1-*b*][1,3]oxazine (3h)

Yield: 896 mg (80%); colorless crystals; mp 206–208 °C (EtOH).

IR (KBr): 3053, 2926, 2899, 2845, 1599, 1560, 1526, 1503, 1449, 1423, 1290, 1258, 1211, 1115, 989, 889, 829, 808, 799, 737, 714 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.35–7.38 (m, 2 H, H-6, 8), 7.20 (d, *J* = 8.2 Hz, 1 H, H-5), 5.27 (s, 2 H, CH_2), 2.03 (br s, 3 H, CH, Ad), 1.80–1.83 (m, 6 H, CH_2, Ad), 1.66–1.73 (m, 6 H, CH_2, Ad).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 154.0 (C), 148.7 (C), 145.7 (C), 137.1 (C), 126.4 (CH), 124.5 (CH), 116.9 (CH), 115.4 (C), 46.4 (CH_2N), 43.1 (3 × CH_2, Ad), 36.6 (3 × CH_2, Ad), 36.1 (C, Ad), 28.8 (3 × CH, Ad).

Anal. Calcd for $C_{19}H_{20}BrN_3O$: C, 59.08; H, 5.22; N, 10.88. Found: C, 59.16; H, 5.26; N, 10.82.

Methyl 2-Bromo-9*H*-benzo[*e*][1,2,4]triazolo[5,1-*b*][1,3]oxazine-7-carboxylate (3i)

Yield: 216 mg (24%); colorless crystals; mp 251–253 °C (EtOAc).

IR (KBr): 3043, 2955, 1717, 1597, 1558, 1524, 1497, 1439, 1300, 1277, 1250, 1195, 1177, 1126, 991, 914, 768 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.03 (d, J = 1.8 Hz, 1 H, H-8), 7.93 (dd, J = 8.7, 1.8 Hz, 1 H, H-6), 7.42 (d, J = 8.7 Hz, 1 H, H-5), 5.35 (s, 2 H, CH_2), 3.84 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.6 (C), 153.6 (C), 151.2 (C), 137.2 (C), 130.9 (CH), 129.9 (CH), 127.0 (C), 117.9 (CH), 117.1 (C), 52.9 (CH_3), 46.2 (CH_2N).

Anal. Calcd for $C_{11}H_8BrN_3O_3$: C, 42.60; H, 2.60; N, 13.55. Found: C, 42.70; H, 2.55; N, 13.59.

2-Bromo-7-methoxy-9*H*-benzo[*e*][1,2,4]triazolo[5,1-*b*][1,3]oxazine (3j)

Yield: 589 mg (72%); colorless crystals; mp 214–216 °C (EtOH).

IR (KBr): 2993, 2939, 2839, 1597, 1562, 1520, 1497, 1435, 1292, 1265, 1234, 1196, 1038, 879, 802, 717 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.22 (dd, J = 6.4, 3.2 Hz, 1 H, H-6), 6.92–6.96 (m, 2 H, H-5, 8), 5.28 (s, 2 H, CH_2), 3.75 (s, 3 H, CH_3O).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.8 (C), 154.0 (C), 141.6 (C), 137.1 (C), 118.4 (CH), 116.9 (C), 115.8 (CH), 112.2 (CH), 56.2 (CH_3), 46.3 (CH_2N).

Anal. Calcd for $C_{10}H_8BrN_3O_2$: C, 42.58; H, 2.86; N, 14.90. Found: C, 42.64; H, 2.80; N, 14.87.

5-(Adamantan-1-yl)-2-bromo-7-methyl-9*H*-benzo[*e*][1,2,4]triazolo[5,1-*b*][1,3]oxazine (3k)

Yield: 975 mg (84%); colorless crystals; mp 241–242 °C (EtOH–DMF, 4:1).

IR (KBr): 2916, 2847, 1609, 1558, 1547, 1462, 1427, 1265, 1200, 1150, 1130, 852, 710 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.06 (s, 1 H, Ar), 7.00 (s, 1 H, Ar), 5.25 (s, 2 H, CH_2), 2.26 (s, 3 H, CH_3), 2.04 (br s, 9 H, CH_2, Ad, CH, Ad), 1.73 (br s, 6 H, CH_2, Ad).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 153.6 (C), 145.0 (C), 137.8 (C), 137.3 (C), 134.7 (C), 127.9 (CH), 126.2 (CH), 116.2 (C), 46.2 (CH_2N), 40.9 (3 × CH_2, Ad), 37.1 (C, Ad), 36.8 (3 × CH_2, Ad), 28.8 (3 × CH, Ad), 21.1 (CH_3).

Anal. Calcd for $C_{20}H_{22}BrN_3O$: C, 60.01; H, 5.54; N, 10.50. Found: C, 59.92; H, 5.60; N, 10.60.

5-(Adamantan-2-yl)-2-bromo-9*H*-benzo[*e*][1,2,4]triazolo[5,1-*b*][1,3]oxazine (3l)

Yield: 884 mg (79%); colorless crystals; mp 228–229 °C (EtOH).

IR (KBr): 2905, 2847, 1558, 1518, 1472, 1443, 1408, 1287, 1250, 1215, 1169, 988, 885, 781, 768, 716 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.47 (d, J = 7.3 Hz, 1 H, Ar), 7.19–7.26 (m, 2 H, Ar), 5.29 (s, 2 H, CH_2), 3.25 (s, 1 H, Ad), 2.26 (s, 2 H, Ad), 1.82–1.97 (m, 8 H, Ad), 1.72 (s, 2 H, Ad), 1.59 (d, J = 12.4 Hz, 2 H, Ad).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 153.9 (C), 146.2 (C), 137.1 (C), 133.6 (C), 128.2 (CH), 125.7 (CH), 125.2 (CH), 116.0 (C), 46.1 (CH_2N), 43.6 (CH_2, Ad), 39.9 (2 × CH_2, Ad), 37.8 (CH_2, Ad), 32.8 (2 × CH_2, Ad), 31.3 (2 × CH, Ad), 27.9 (CH, Ad), 27.4 (CH, Ad).

Anal. Calcd for $C_{19}H_{20}BrN_3O$: C, 59.08; H, 5.22; N, 10.88. Found: C, 59.15; H, 5.16; N, 10.93.

2-Bromo-7-nitro-9*H*-benzo[*e*][1,2,4]triazolo[5,1-*b*][1,3]oxazine (3m)

Yield: 551 mg (64%); light-yellow crystals; mp 236–238 °C (EtOH–MeCN, 1:2).

IR (KBr): 1597, 1557, 1518, 1479, 1404, 1346, 1287, 1217, 1184, 1150, 1084, 930, 893, 839, 820, 748, 716, 656 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.40 (d, J = 2.8 Hz, 1 H, H-8), 8.23 (dd, J = 2.8, 9.2 Hz, 1 H, H-6), 7.54 (d, J = 9.2 Hz, 1 H, H-5), 5.38 (s, 3 H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 153.3 (C), 152.3 (C), 144.6 (C), 137.3 (C), 125.4 (CH), 124.5 (CH), 118.8 (CH), 118.3 (C), 46.4 (CH_2).

Anal. Calcd for $C_9H_5BrN_4O_3$: C, 36.39; H, 1.70; N, 18.86. Found: C, 36.44; H, 1.78; N, 19.79.

Ethyl 8-Bromo-2-methyl-3,11-dihydro[1,2,4]triazolo[5′,1′:2,3][1,3]oxazino[5,6-*e*]indole-1-carboxylate (3n)

Yield: 427 mg (39%); white crystals; mp 269–270 °C (DMF).

IR (KBr): 3300–3100, 2978, 2932, 1701, 1570, 1520, 1477, 1435, 1385, 1288, 1215, 1200, 1150, 1092, 1057, 1030, 991, 802, 783 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.09 (br s, 1 H, NH), 7.36 (d, J = 8.7 Hz, 1 H, Ar), 7.04 (d, J = 8.7 Hz, 1 H, Ar), 5.64 (s, 2 H, CH_2), 4.24 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 2.57 (s, 3 H, CH_3), 1.32 (t, J = 7.1 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.1 (C=O), 153.5 (C), 146.3 (C), 143.2 (C), 137.1 (C), 132.7 (C), 123.2 (C), 112.9 (CH), 112.5 (CH), 106.7 (C), 105.3 (C), 60.1 (CH_2), 47.0 (CH_2), 15.3 (CH_3), 14.8 (CH_3).

Anal. Calcd for $C_{15}H_{13}BrN_4O_3$: C, 47.76; H, 3.47; N, 14.85. Found: C, 47.84; H, 3.55; N, 14.81.

2,9-Dibromo-6,13-dihydrobis[1,2,4]triazolo[5,1-*b*:5,1-*b*′]benzo[1,2-*e*:4,5-*e*′]bis[1,3]oxazine (3o)

The title compound was synthesized by the general procedure using 2 equiv of **1**; yield: 890 mg (72%); colorless crystals; mp >350 °C (DMF, dec.).

IR (KBr): 3063, 2935, 1562, 1528, 1501, 1440, 1404, 1327, 1300, 1281, 1242, 1196, 1161, 1134, 987, 914, 887, 729, 717 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6 at 100 °C): δ = 7.39 (s, 2 H, Ar), 5.35 (s, 4 H, 2 × CH_2).

^{13}C NMR (100 MHz, DMSO-d_6 at 145 °C): δ = 154.1 (2 C), 154.1 (2 C) 137.4 (2 C), 117.9 (2 × CH), 116.4 (2 C), 46.3 (2 × CH_2).

Anal. Calcd for $C_{12}H_6Br_2N_6O_2$: C, 33.83; H, 1.42; N, 19.73. Found: C, 33.88; H, 1.51; N, 19.68.

5-(Adamantan-1-yl)-7-methyl-9*H*-benzo[*e*][1,2,4]triazolo[5,1-*b*][1,3]oxazine (3p)

The title compound was synthesized by the general procedure using 3-chloro-1,2,4-triazole; yield: 652 mg (70%); colorless crystals; mp 197–199 °C (EtOH).

IR (KBr): 3109, 2916, 2847, 1612, 1558, 1547, 1462, 1427, 1265, 1242, 1200, 1150, 1130, 868, 856 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.81 (s, 1 H, H-2), 7.01 (s, 1 H) and 7.05 (s, 1 H) (H-6, 8), 5.30 (s, 2 H, CH_2), 2.26 (s, 3 H, CH_3), 2.06 (br s, 9 H, CH Ad, CH_2, Ad), 1.73 (br s, 6 H, CH_2, Ad).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 153.5 (C), 149.5 (CH-2), 145.4 (C), 137.8 (C), 134.3 (C), 127.8 (CH), 126.2 (CH), 116.3 (C), 46.0 (CH_2N), 40.8 (3 × CH_2, Ad), 37.1 (C, Ad), 36.8 (3 × CH_2, Ad), 28.8 (3 × CH, Ad), 21.0 (CH_3).

MS (EI): m/z (%) = 321 (100, $[M]^+$), 320 (22, $[M - H]^+$), 278 (8), 264 (62), 236 (17), 228 (15), 221 (7), 200 (11), 165 (16).

Anal. Calcd for $C_{20}H_{23}N_3O$: C, 74.74; H, 7.21; N, 13.07. Found: C, 74.80; H, 7.17; N, 13.01.

2-Bromo-7-chloro-5-[(3,5-dibromo-1*H*-1,2,4-triazol-1-yl)methyl]-9*H*-benzo[*e*][1,2,4]triazolo[5,1-*b*][1,3]oxazine (3q)

3,5-Dibromo-1,2,4-triazole (**1**; 1.134 g, 5.0 mmol) and 4-chloro-2,6-bis(hydroxymethyl)phenol (**2q**; 472 mg, 2.5 mmol) were refluxed for 5 h in DMF (10 mL). After completion of the reaction, the mixture was cooled and poured into H_2O (30 mL). The precipitate formed was collected by filtration, washed with H_2O, dried, and recrystallized; yield: 722 mg (55%); colorless crystals; mp 258–260 °C (DMF).

IR (KBr): 2924, 1601, 1555, 1520, 1470, 1431, 1292, 1261, 1180, 1150, 1065, 987, 864 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.58 (d, *J* = 2.3 Hz 1 H, Ar), 7.50 (d, *J* = 2.3 Hz, 1 H, Ar), 5.47 (s, 2 H, CH_2), 5.29 (s, 2 H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 153.2 (C), 145.0 (C), 140.3 (C), 137.2 (C), 132.2 (C), 130.6 (CH), 129.2 (C), 128.4 (CH), 124.9 (C), 119.0 (C), 48.0 (CH_2), 46.1 (CH_2).

MS for ^{79}Br, ^{35}Cl (EI): *m*/*z* (%) = 522 (2, $[M]^+$), 443 (2, $[M - Br]^+$), 364 (1, $[M - 2\ Br]^+$), 298 (7, $[M - C_2Br_2N_3]^+$), 218 (5), 177 (5), 156 (21), 153 (23, $[C_8H_6ClO]^+$), 137 (20), 128 (30), 125 (58), 102 (73), 89 (100), 80 (65).

Anal. Calcd for $C_{12}H_6Br_3ClN_6O$: C, 27.43; H, 1.15; N, 16.00. Found: C, 27.51; H, 1.09; N, 16.09.

2-[(3,5-Dibromo-1*H*-1,2,4-triazol-1-yl)methyl]-6-methoxyphenol (4a)

3,5-Dibromo-1,2,4-triazole (**1**; 658 mg, 2.9 mmol) and salicylic alcohol **2c** (447 mg, 2.9 mmol) were refluxed for 2 h in DMF (10 mL). After completion of the reaction, the mixture was cooled and poured into H_2O (30 mL). The precipitate formed was collected by filtration, washed with H_2O, dried, and recrystallized from EtOH; yield: 585 mg (60%); colorless crystals; mp 149–150 °C.

IR (KBr): 3500–3000 (O–H), 1612, 1593, 1553, 1520, 1485, 1468, 1433, 1364, 1290, 1267, 1231, 1184, 1069, 1005, 916, 837, 777, 760, 721, 704 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 9.09 (s, 1 H, OH), 6.91 (dd, *J* = 8.2, 1.2 Hz, 1 H, Ar), 6.73 (t, *J* = 7.9 Hz, 1 H, Ar), 6.57 (d, *J* = 7.6 Hz, 1 H, Ar), 5.26 (s, 2 H, CH_2), 3.75 (s, 6 H, 2 × CH_3O).

^1H NMR (400 MHz, CD_3CN): δ = 6.91 (dd, *J* = 8.0, 1.4 Hz, 1 H, Ar), 6.89 (br s, 1 H, OH), 6.79 (t, *J* = 8.0 Hz, 1 H, Ar), 6.66 (dd, *J* = 7.8, 1.4 Hz, 1 H, Ar), 5.27 (s, 2 H, CH_2), 3.82 (s, 6 H, 2 × CH_3O).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 148.0 (C), 144.8 (C), 139.6 (C), 131.7 (C), 121.5 (C, CH), 119.5 (CH), 112.4 (CH), 56.4 (2 × CH_3), 49.2 (CH_2).

^{13}C NMR (100 MHz, CD_3CN): δ = 147.2 (C), 144.2 (C), 139.4 (C), 130.5 (C), 121.4 (CH), 120.3 (C), 119.7 (CH), 111.7 (CH), 55.9 (2 × CH_3), 48.7 (CH_2).

Anal. Calcd for $C_{10}H_9Br_2N_3O_2$: C, 33.09; H, 2.50; N, 11.58. Found: C, 32.95; H, 2.41; N, 11.45.

5-[(3,5-Dibromo-1*H*-1,2,4-triazol-1-yl)methyl]-6-hydroxy-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-one (4b)

3,5-Dibromo-1,2,4-triazole (**1**; 658 mg, 2.9 mmol) and Mannich base **2p** (752 mg, 2.9 mmol) were refluxed for 2 h in EtOH (10 mL). Product was isolated analogously to compound **4a**; yield: 475 mg (59%); colorless crystals; mp 199–200 °C (EtOH).

IR (KBr): 3309, 3240, 1643, 1582, 1539, 1512, 1454, 1427, 1369, 1346, 1300, 1261, 1204, 1084, 1045, 930, 810, 775 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 11.46 (s, 1 H, NH), 9.21 (s, 1 H, OH), 7.52 (s, 1 H, NHCO), 7.22 (d, *J* = 8.7 Hz, 1 H, Ar), 6.78 (d, *J* = 8.7 Hz, 1 H, Ar), 5.48 (s, 2 H, CH_2N), 3.45 (td, *J* = 6.9, 2.3 Hz, 2 H, CH_2), 3.01 (t, *J* = 6.9 Hz, 2 H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.3 (C=O), 150.4 (C), 139.4 (C), 132.5 (C), 131.3 (C), 128.8 (C), 125.7 (C), 117.1 (C), 115.0 (CH), 114.5 (CH), 110.3 (C), 46.0 (CH_2), 41.5 (CH_2), 22.8 (CH_2).

Anal. Calcd for $C_{14}H_{11}Br_2N_5O_2$: C, 38.12; H, 2.51; N, 15.88. Found: C, 38.05; H, 2.46; N, 15.92.

1-(6,8-Di-*tert*-butylchroman-2-yl)pyrrolidin-2-one (6)

Mannich base **2d** (1 g, 3.8 mmol) and *N*-vinyl-2-pyrrolidone (0.5 mL, 0.48 g, 4.3 mmol) in DMF (10 ml) were refluxed for 12 h. After completion of the reaction, the solution was cooled and poured into H_2O (30 mL). The precipitate formed was collected by filtration, washed with H_2O, dried, and recrystallized from MeOH; yield: 0.9 g (72%); colorless crystals; mp 134–135 °C.

IR (KBr): 2955, 2924, 2872 (C–H *t*-Bu), 1701 (C=O), 1476, 1458, 1449, 1423, 1362, 1321, 1288, 1221, 1200, 1167, 1125, 1098, 1045, 1003 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.16 (d, *J* = 2.3 Hz, 1 H, Ar), 6.93 (d, *J* = 2.3 Hz, 1 H, Ar), 5.87 (dd, *J* = 11.0, 2.3 Hz, 1 H, CHNO), 3.58–3.64 (m, 1 H), 3.46–3.52 (m, 1 H), 3.07 (ddd, *J* = 16.5, 12.4, 6.4 Hz, 1 H), 2.85 (ddd, *J* = 16.5, 5.5, 2.3 Hz, 1 H), 2.49 (t, *J* = 8.2 Hz, 2 H), 2.05–2.17 (m, 3 H), 1.96–2.01 (m, 1 H), 1.36 (s, 9 H, *t*-C_4H_9), 1.29 (s, 9 H, *t*-C_4H9).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.6 (C=O), 150.8 (C–O), 142.5 (C), 137.0 (C), 123.9 (CH), 122.1 (CH), 120.2 (C), 78.0 (CHNO), 42.7 (CH_2), 35.1 (C), 34.3 (C), 31.7 [$C(CH_3)_3$] , 30.0 [$C(CH_3)_3$] , 25.9 (CH_2), 25.5 (CH_2), 18.5 (CH_2).

MS (EI): *m*/*z* (%) = 329 (55, $[M]^+$), 314 (11, $[M - CH_3]^+$), 244 (65, $[M - C_4H_7NO]^+$), 229 (100, $[M - CH_3 - C_4H_7NO]^+$), 203 (47, $[M - C_6H_9NO - CH_3]^+$), 187 (45), 98 (32), 57 (12, $[Me_3C]^+$).

Anal. Calcd for $C_{21}H_{31}NO_2$: $C_{21}H_{31}NO_2$. Found: C, 76.48; H, 9.59; N, 4.13.

4-[(3,5-Dibromo-1*H*-1,2,4-triazol-1-yl)methyl]phenols 8; General Procedure

3,5-Dibromo-1,2,4-triazole (**1**; 658 mg, 2.9 mmol) and *p*-quinone methide precursor **7** (2.9 mmol) were refluxed for 4 h in DMF (10 mL). Products were isolated analogously to compound **4a**.

4-[(3,5-Dibromo-1*H*-1,2,4-triazol-1-yl)methyl]-2-ethoxyphenol (8a)

Yield: 864 mg (79%); colorless crystals; mp 125–127 °C (EtOH).

IR (KBr): 3500–3000 (OH), 2980, 1603, 1530, 1454, 1435, 1414, 1393, 1352, 1271, 1223, 1161, 1126, 1069, 1036 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 9.04 (s, 1 H, OH), 6.85 (d, *J* = 1.6 Hz, 1 H, H-3), 6.73 (d, *J* = 8.0 Hz, 1 H, H-5), 6.63 (dd, *J* = 8.0, 1.6 Hz, 1 H, H-6), 5.22 (s, 2 H, CH_2N), 3.95 (q, *J* = 7.2 Hz, 2 H, CH_2CH_3), 1.28 (t, *J* = 7.2 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 147.5 (C), 147.2 (C), 139.8 (C), 131.0 (C), 125.7 (C), 121.2 (CH), 116.2 (CH), 114.1 (CH), 64.4 (CH_2), 53.5 (CH_2), 15.2 (CH_3).

MS for ^{79}Br (EI): *m*/*z* (%) = 375 (14, $[M]^+$), 151 (100, $[M - C_2Br_2N_3]^+$), 123 (90, $[M - C_2Br_2N_3 - C_2H_4]^+$), 122 (26).

Anal. Calcd for $C_{11}H_{11}Br_2N_3O_2$: C, 35.04; H, 2.94; N, 11.14. Found: C, 34.95; H, 2.88; N, 11.19.

4-[(3,5-Dibromo-1*H*-1,2,4-triazol-1-yl)methyl]-2,6-dimethoxyphenol (8b)

Yield: 707 mg (62%); colorless crystals; mp 154–156 °C (EtOH).

IR (KBr): 3500–3100 (OH), 3011, 2967, 2940, 2841, 1616, 1591, 1520, 1458, 1431, 1375, 1356, 1329, 1263, 1244, 1223, 1190, 1159, 1117, 1076, 1042, 827, 770 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.51 (br s, 1 H, OH), 6.55 (s, 2 H, H-3, 5), 5.23 (s, 2 H, CH_2), 3.70 (s, 6 H, 2 × CH_3O).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 148.6 (2 C), 139.8 (C), 136.3 (C), 131.1 (C), 124.8 (C), 106.3 (2 × CH), 56.6 (2 × CH_3), 53.8 (CH_2).

MS for ^{79}Br (EI): *m*/*z* (%) = 391 (14, $[M]^+$), 167 (100, $[M - C_2Br_2N_3]^+$).

Anal. Calcd for $C_{11}H_{11}Br_2N_3O_3$: C, 33.62; H, 2.82; N, 10.69. Found: C, 33.71; H, 2.76; N, 10.75.

4-[(3,5-Dibromo-1*H*-1,2,4-triazol-1-yl)methyl]-2,6-dimethylphenol (8c)

Yield: 838 mg (80%); colorless crystals; mp 185–186 °C (EtOH).

IR (KBr): 3500–3200 (O–H), 16.3, 1489, 1452, 1427, 1383, 1354, 1337, 1312, 1273, 1211, 1155, 1069, 962, 876, 768 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.36 (s, 1 H, OH), 6.82 (s, 2 H, H-3, 5), 5.16 (s, 2 H, CH_2), 2.11 (s, 6 H, 2 × CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 153.9 (C), 139.8 (C), 130.8 (C), 128.5 (2 × CH), 125.3 (2 C), 125.1 (C), 53.3 (CH_2), 17.1 (2 × CH_3).

MS for ^{79}Br (EI): *m*/*z* (%) = 359 (10, $[M]^+$), 135 (100, $[M - C_2Br_2N_3]^+$), 91 (15).

Anal. Calcd for $C_{11}H_{11}Br_2N_3O$: C, 36.59; H, 3.07; N, 11.64. Found: C, 36.62; H, 3.00; N, 11.71.

9*H*-Benzo[*e*]pyrazolo[5,1-*b*][1,3]oxazines 10; General Procedure

3,4,5-Tribromopyrazole (**9a**; 762 mg, 2.5 mmol) or 3,5-dibromo-4-nitropyrazole (**9b**; 677 mg, 2.5 mmol), *o*-quinone methide precursor **2** (2.5 mmol) and K_2CO_3 (only for **9a**, 1.035 g, 7.5 mmol) were refluxed for 4 h in DMF (10 mL). Product was isolated analogously to compound **4a**.

(2,3-Dibromo-7-methoxy-9*H*-benzo[*e*]pyrazolo[5,1-*b*][1,3]oxazin-5-yl)methanol (10a)

Yield: 634 mg (65%); colorless crystals; mp 229–230 °C (MeOH–DMF, 3:1).

IR (KBr): 3500–3300, 2931, 2870, 2839, 1624, 1609, 1570, 1531, 1481, 1435, 1389, 1358, 1234, 1188, 1142, 1084, 1045, 1022, 891, 856, 737 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 6.98 (s, 1 H, Ar), 6.79 (s, 1 H, Ar), 5.36 (br s, 1 H, OH), 5.21 (s, 2 H, CH_2), 4.58 (s, 2 H, CH_2OH), 3.72 (s, 3 H, CH_3O).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.2, 145.7, 138.1, 132.1, 127.1, 116.5, 113.6, 110.0, 76.0 (C-3), 57.4, 56.0, 46.7 (CH_2N).

MS for ^{79}Br (EI): *m*/*z* (%) = 388 (22, $[M]^+$), 309 (5, $[M - Br]^+$), 164 (20), 149 (37), 121 (94), 107 (27), 91 (38, $[C_7H_7]^+$), 77 (100).

Anal. Calcd for $C_{12}H_{10}Br_2N_2O_3$: C, 36.95; H, 2.58; N, 7.18. Found: 37.01; H, 2.52; N, 7.09.

7-(1-Adamantyl)-2,3,5-tribromo-9*H*-benzo[*e*]pyrazolo[5,1-*b*][1,3]oxazine (10b)

Yield: 719 mg (53%); colorless crystals; mp 212–214 °C (MeOH–DMF, 3:1).

IR (KBr): 2924, 2901, 2847, 1566, 1528, 1470, 1450, 1385, 1358, 1315, 1269, 1223, 1130, 1011, 895, 868 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 1.8 Hz, 1 H, Ar), 7.11 (d, *J* = 1.8 Hz, 1 H, Ar), 5.25 (s, 2 H, CH_2), 2.11 (br s, 3 H, CH, Ad), 1.71–1.86 (m, 12 H, CH_2, Ad).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.6, 145.6, 142.3, 130.5, 128.5, 122.9, 115.8, 110.9, 77.4 (C-3), 46.9 (CH_2N), 43.1, 36.5, 36.2, 28.8.

Anal. Calcd for $C_{20}H_{19}Br_3N_2O$: C, 44.23; H, 3.53; N, 5.16. Found: C, 44.12; H, 3.55; N, 5.06.

2-Bromo-3-nitro-9*H*-benzo[*e*]pyrazolo[5,1-*b*][1,3]oxazine (10c)

Yield: 592 mg (80%); colorless crystals; mp 228–230 °C (DMF).

IR (KBr): 1593, 1562, 1528, 1489, 1454, 1416, 1400, 1354, 1339, 1273, 1246, 1223, 1173, 1107, 1061, 918, 849, 833, 760 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.36–7.44 (m, 3 H, Ar), 7.30 (dd, *J* = 7.8, 1.4 Hz, 1 H, Ar), 5.30 (s, 2 H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 146.6 (C), 145.5 (C), 130.2 (CH), 128.4 (CH), 126.5 (CH), 123.0 (C), 117.3 (CH), 116.4 (C-3), 116.0 (C), 46.3 (CH_2N).

Anal. Calcd for $C_{10}H_6BrN_3O_3$: C, 40.57; H, 2.04; N, 14.19. Found: C, 40.63; H, 1.99; N, 14.03.

2,7-Dibromo-3-nitro-9*H*-benzo[*e*]pyrazolo[5,1-*b*][1,3]oxazine (10d)

Yield: 703 mg (75%); light-yellow crystals; mp 244–246 °C (DMF).

IR (KBr): 3055, 1593, 1562, 1528, 1501, 1477, 1420, 1400, 1350, 1250, 1173, 1115, 1065, 918, 833 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.67 (d, *J* = 2.3 Hz, 1 H, H-8), 7.58 (dd, *J* = 8.7, 2.3 Hz, 1 H, H-6), 7.34 (d, *J* = 8.7 Hz, 1 H, H-5), 5.27 (s, 2 H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 146.0 (C), 145.1 (C), 132.8 (CH), 130.9 (CH), 123.1 (C), 119.5 (CH), 118.6 (C), 118.0 (C), 116.5 (C-3), 46.1 (CH_2N).

MS for ^{79}Br (EI): *m*/*z* (%) = 373 (32, $[M]^+$), 343 (4, $[M - NO]^+$), 294 (2, $[M - Br]^+$), 210 (50), 184 (25), 156 (18, $[C_6H_5Br]^+$), 131 (32), 113 (58), 89 (38), 77 (100, $[C_6H_5]^+$).

Anal. Calcd for $C_{10}H_5Br_2N_3O_3$: C, 32.03; H, 1.34; N, 11.21. Found: C, 31.92; H, 1.28; N, 11.19.

7-Nitro-5*H*-benzo[*e*]imidazo[2,1-*b*][1,3]oxazines 12; General Procedure

Imidazole **11a** or **11b** (1.2 mmol) and *o*-quinone methide precursor **2m** (303 mg, 2.5 mmol) were refluxed for 4 h in a mixture of H_2O (1.5 mL) and MeCN (3 mL). Product was isolated analogously to compound **4a**.

7-Nitro-5*H*-benzo[*e*]imidazo[2,1-*b*][1,3]oxazine-2,3-dicarbonitrile (12a)

Yield: 151 mg (47%); yellow crystals; mp 258–260 °C (MeCN–H_2O, 2:1, dec.).

IR (KBr): 3074, 3047, 2928, 2233 (C≡N), 1597, 1547, 1535 (NO_2), 1504, 1481, 1350 (NO_2), 1319, 1304, 1273, 1223, 1188, 1130, 1092, 930, 868, 852, 748, 706 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.46 (d, *J* = 2.7 Hz, 1 H, H-6), 8.25 (dd, *J* = 9.2, 2.7 Hz, 1 H, H-8), 7.57 (d, *J* = 9.2 Hz, 1 H, H-9), 5.48 (s, 2 H, CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 151.8 (C), 147.8 (C), 144.9 (C), 125.7 (CH), 124.2 (CH), 118.7 (CH), 118.3 (C), 116.5 (C), 112.6 (C), 108.8 (CN), 108.6 (CN), 44.6 (CH_2).

Anal. Calcd for $C_{12}H_5N_5O_3$: C, 53.94; H, 1.89; N, 26.21. Found: C, 53.88; H, 1.83; N, 26.13.

Dimethyl 7-Nitro-5*H*-benzo[*e*]imidazo[2,1-*b*][1,3]oxazine-2,3-dicarboxylate (12b)

Yield: 228 mg (57%); light-yellow crystals; mp 227–229 °C (MeCN–H_2O, 2:1, dec.).

IR (KBr): 3047, 1751 (C=O), 1713 (C=O), 1555, 1543 (NO_2), 1501, 1485, 1342 (NO_2), 1304, 1261, 1219, 1165, 1088, 1068, 899, 806, 748 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.43 (d, *J* = 2.5 Hz, 1 H, H-6), 8.20 (dd, *J* = 9.0, 2.5 Hz, 1 H, H-8), 7.48 (d, *J* = 9.0 Hz, 1 H, H-9), 5.47 (s, 2 H, CH_2), 3.82 (s, 3 H, CH_3), 3.78 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.2 (C=O), 159.4 (C=O), 152.3 (C), 146.8 (C), 144.4 (C), 134.1 (C), 125.3 (CH), 124.4 (CH), 119.5 (C), 118.3 (CH), 117.7 (C), 52.8 (2 × CH_3), 45.2 (CH_2).

Anal. Calcd for $C_{14}H_{11}N_3O_7$: C, 50.46; H, 3.33; N, 12.61. Found: C, 50.41; H, 3.28; N, 12.72.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588411.

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