Bioorganic & Medicinal Chemistry Letters 21 (2011) 3117–3121

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Synthesis and antiproliferative activity of new cytotoxic azanaphthoquinone pyrrolo-annelated derivatives: Part II ☆

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ARTICLE INFO

Article history:
Received 12 January 2011
Revised 2 March 2011
Accepted 3 March 2011
Available online 9 March 2011

Keyword:
Anticancer compounds

ABSTRACT

A series of 6-azanaphthoquinone pyrrolo-annelated derivatives carrying different basic side chains have been synthesized. The antiproliferative activities of all compounds were evaluated on at least four different cell lines with Mitoxantrone as reference compound. Cytotoxic effects and DNA intercalation behavior were investigated.

Mitoxantrone is one of the most widely used therapeutics in combating a variety of cancerous diseases.[2,3] Due to cardiotoxicity[4] another less cardiotoxic compound, namely aza-anthracene-9,10-dione BBR2778 (Pixantrone) was developed, which is currently in phase III of clinical trials in patients with non-Hodgkin's lymphoma.[5] Based on this type of compounds we synthesized a series of new potential cytotoxic derivatives. In these compounds the bis-amino phenyl ring was replaced by a mono- or bis-substituted pyrrole ring. As reported previously by the authors, the position of the nitrogen in the annelated pyridine[1] and pyrrole[6] ring has also drastic effects on the antitumor activity. Hence, we investigated a series of new 6-azanaphthoquinone pyrrolo-annelated compounds derived from Pixantrone with position 3 of the pyrrole ring either unsubstituted (**1**), or dimethylaminoethyl or -propyl substituted (**2**), respectively. In this paper, we discuss the influence of different side chains on the antiproliferative effects, which are attached to the pyrrole nitrogen in position 1 and 3 leading to key structures **1** and **2** (Fig. 1). The side chains attached to the tricyclic nucleus were predominantly provided with alkylating groups (oxiranyl, aziridinyl, mesylate) and/or amino groups. As a consequence, alkylation should lead to irreversible drug–DNA bonds. Furthermore, side chains with amino groups can enhance binding to the double-helical DNA by interaction with its phosphate 'back bone'.

Main core **1** was prepared according to a method previously reported by the authors.[7] The first step of the synthesis of compounds **3–5** consisted of the alkylation of **1** with the according bromoalkoxy-*tert*-butyl-diphenylsilanes to give **15–17**. Deprotection to obtain alcohols **18–20** (n = 2, 4, 7) was carried out by treatment with tetrabutylammoniumfluoride (TBAF) in THF. Alcohols **18–20** were reacted with mesylchloride to afford the compounds **3–5**, which were converted into aziridines **6–8** by treatment with aziridine and triethylamine in DCM. Compounds **9–11** were obtained by deprotonation of compound **1** with NaH and reaction with the corresponding haloalkyloxirane. The synthesis of products 12–14 was accomplished by treatment of oxiranes **9–11** with aziridine in a solution of triethylamine (1%) in absolute ethanol (Scheme 1).

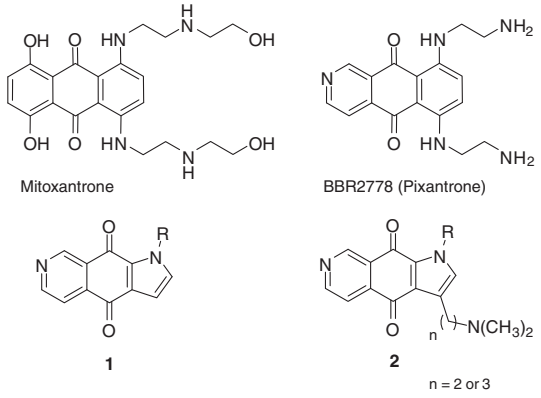

Figure 1.

☆ See Ref. 1.

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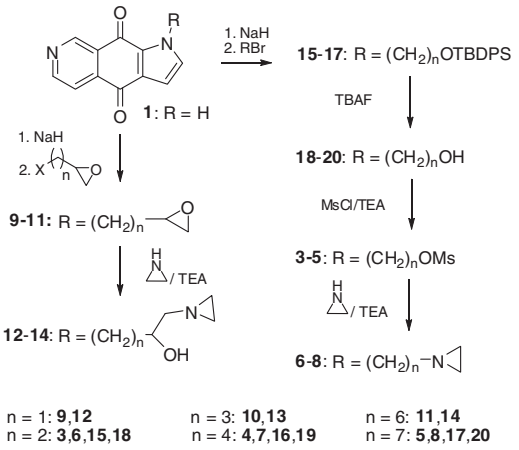
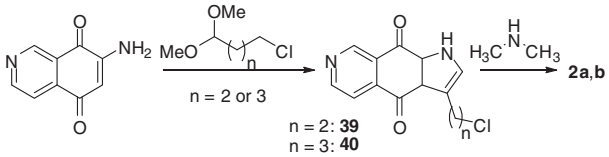
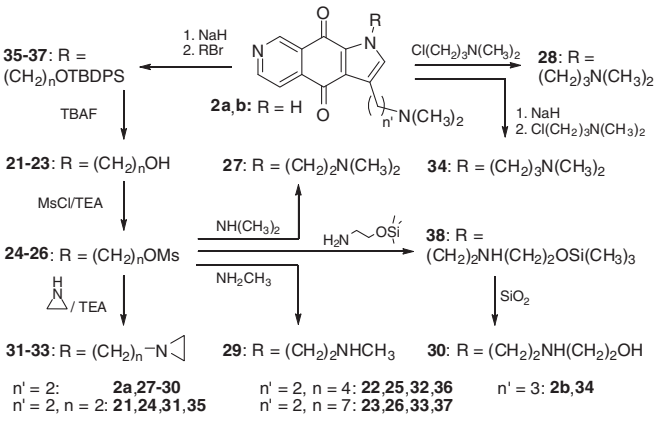
doi:10.1016/j.bmcl.2011.03.013



Scheme 1.



Scheme 2.



Scheme 3.

7-Aminoisoquinoline-5,8-dione[7] was reacted with either chlorobutyraldehyde-dimethylacetal or 5-chloro-1,1-dimethoxypentane yielding **39** and **40**, respectively, which afforded **2a** and **2b** upon treatment with *N*,*N*-dimethylamine (Scheme 2).

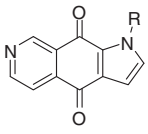
Alcohols **21**–**23** were prepared by reaction of TBAF with the appropriate *tert*-butyldiphenylsilyl (TBDPS) protected precursors **35**–**37** which were obtained by treating deprotonated **2a**,**b** with the according bromoalkoxy-*tert*-butyldiphenylsilanes. Mesylation of alcohols **21**–**23** gave compounds **24**–**26** which served as precursors for aziridines **31**–**33**, dimethylamines **27**, monomethylamine **29**, and trimethylsilyloxyethylamine **38**. Deprotection of **38** occurred spontaneously during column chromatography on silica gel to afford hydroxyethylamine **30**. Compounds **28** and **34** were prepared directly by alkylation of **2a** or **2b** with *N*,*N*-dimethyl chloropropylamine (Scheme 3).

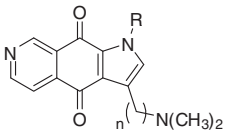
Pyrrole annelated 6-azanaphthoquinones (except the instable mesylates **25** and **26**) were screened for antiproliferative activity against different cancer cell lines KB/HeLa (cervical carcinoma), SKOV-3 (ovarian carcinoma), SF-268 (CNS, glioma), NCI-H460 (non-small cell lung carcinoma (NSCLC)), and of RKOp27 (colon adenocarcinoma).[8]

The concentration of the compound that inhibits 50% (EC_{50}) of cell proliferation after 48 h was calculated by nonlinear regression using the data of at least two independent XTT cytotoxicity assays.[9,10] Results of the cytotoxicity assays are shown in detail in Table 2 together with Mitoxantrone as reference.

9 is the most antiproliferative compound (EC_{50}(KB/HeLa)[b]: 0.062 μg/ml) that has been reported on the series of Mitoxantrone derived azanaphtho-chinones so far.[5,7] Its activity profile is significantly different as EC_{50} values are 8–12 times higher than for the next best new compound, **7**. Activity is better or in the same range compared to reference compound Mitoxantrone. This antiproliferative property is assigned to the oxiran group connected by a C1-spacer. Compounds **10** and **11** contain also oxirane groups, but are linked through longer spacers and show no activity.

Table 1





1: R = H	**10**: R = $(CH_2)_3$–O	*n* = 2	**2a**:R = H	**27**:R = $(CH_2)_2N(CH_3)_2$
3: R = $(CH_2)_2OMs$	**11**: R = $(CH_2)_6$–O		**21**:R = $(CH_2)_2OH$	**28**:R = $(CH_2)_3N(CH_3)_2$
4: R = $(CH_2)4OMs$	**12**: R = CH_2–N, OH		**22**:R = $(CH_2)_4OH$	**29**:R = $(CH_2)_2NHCH_3$
5: R = $(CH_2)_7OMs$	**13**: R = $(CH_2)_3$–N, OH		**23**:R = $(CH_2)_7OH$	**30**:R = $(CH_2)_2NH(CH_2)_2OH$
6: R = $(CH_2)_2$–N	**14**: R = $(CH_2)_6$–N, OH		**24**:R = $(CH_2)_2OMs$	**31**: R = $(CH_2)_2$–N
7: R = $(CH_2)_4$–N			**25**:R = $(CH_2)_4OMs$	**32**: R = $(CH_2)_4$–N
8: R = $(CH_2)_7$–N			**26**:R = $(CH_2)_7OMs$	**33**: R = $(CH_2)_7$–N
9: R = CH_2–O		*n* = 3	**2b**:R = H	**34**:R = $(CH_2)_3N(CH_3)_2$

Table 2
In vitro cytotoxicity of compounds **2a–14**, **21–34**, **39** and **40** towards different cell lines

Cells (origin)/compound	Compound activity (EC_{50} [μg/mL][a])					
	KB/HeLa[b] (cervix)	SKOV-3 (ovarian)	SF-268 (CNS)	NCI-H460 (NSCLC)	RKOp27 (colon)	RKOp27IND (colon)
2a, 5, 11, 22–24, 27	No inhib.[c]	No inhib.	No inhib.	No inhib.	No inhib.	No inhib.
2b	No inhib.	No inhib.	No inhib.	Moderate[d]	No inhib.	No inhib.
3	No inhib.	No inhib.	No inhib.	Moderate	No inhib.	No inhib.
4	Moderate	No inhib.	Moderate	Moderate	Moderate	No inhib.
6	Moderate	No inhib.	Moderate	Moderate	Moderate	Moderate
7	0.549 ± 0.23 (5)	2.185 ± 0.52 (3)	1.894 ± 0.22 (5)	0.727 ± 0.28 (5)	0.299 ± 0.05 (5)	2.231 (1)
8	Moderate	Moderate	Moderate	Moderate	1.194 (1)	Moderate
9	0.062 ± 0.01 (5)	0.265 ± 0.03 (5)	0.2 ± 0.041 (5)	0.062 ± 0.005 (5)	0.026 ± 0.006 (5)	1.3 ± 0.846 (4)
10	Moderate	No inhib.	No inhib.	Moderate	Moderate	No inhib.
12	0.747 (1)	Moderate	Moderate	2.213 (1)	0.899 (1)	Moderate
13	Moderate	No inhib.	No inhib.	Moderate	Moderate	No inhib.
14	Moderate	No inhib.	No inhib.	Moderate	Moderate	No inhib.
25,26[e]	Not tested	Not tested	Not tested	Not tested	Not tested	Not tested
21	Moderate	No inhib.	No inhib.	No inhib.	Moderate	No inhib.
28, 29	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
30	Moderate	No inhib.	Moderate	No inhib.	Moderate	No inhib.
31	0.972 ± 0.09 (2)	2.739 (1)	2.411 ± 0.44 (2)	Moderate	0.784 ± 0.3 (3)	2.365 ± 0.86 (3)
32	0.512 ± 0.09 (3)	1.510 ± 0.15 (3)	1.392 ± 0.49 (3)	0.722 ± 0.43 (3)	0.205 ± 0.13 (3)	1.35 ± 0.97 (3)
33	Moderate	Moderate	No inhib.	Moderate	Moderate	No inhib.
34	No inhib.	No inhib.	No inhib.	Moderate	Moderate	No inhib.
Mitoxantrone	0.3550 ± 0.137 (5)	0.1207 ± 0.042 (3)	0.3150 ± 0.206 (3)	0.1224 ± 0.013 (3)	0.0865 ± 0.005 (3)	0.7629 ± 0.200 (2)

[a] EC_{50} values <3 μg/ml are given as mean values ± standard deviation with number of replicates given in round brackets.
[b] EC_{50}(KB) denotes the activity for KB/HeLa cell line, which is used to compare compound activities.
[c] No inhib. = no inhibition, that is, <30% inhibition in the highest concentration (3.16 μg/ml) during EC_{50} determination.
[d] 'Moderate' activity describes compound activity, that showed at least 30% inhibition in the highest concentration (3.16 μg/ml) during EC_{50} determination. Since a sigmoidal inhibition-concentration curve is not available, compound activity can only be given as EC_{50} >3.16 μg/ml.
[e] Not tested due to instability.

The difference in activity could be explained by an oxirane ring opening mechanism, that is, alkylation.

Aziridine derivative **32** (EC_{50}(KB/HeLa): 0.512 μg/ml) shows also an interesting antiproliferative activity profile. Compared to **7** (EC_{50}(KB/HeLa): 0.549 μg/ml), the additional dimethylaminoethyl group slightly enhances activity. This activity enhancement by a second side chain is more visible when comparing dimethyl aminoethyl containing compound **31** with **6** (EC_{50}(KB/HeLa): 0.972 and >3.16 μg/ml[c], respectively), though the overall activity of this pair is fair to moderate.

Interestingly, when changing the aziridine group in **31** to a dimethylamino group as in **27**, activity disappears completely. While exposing similar hydrogen bonding properties, the main differences between a dimethyl amino and an aziridine group are alkylation properties of the latter. As with the oxiran **9**, the results could be explained by alkylation as the underlying mechanism of action, which would be contrasting to the mechanism of action of Mitoxantrone. Moreover since tumor environments are known to be acidic the stability of the epoxy moiety (**9–11**) was checked by exposing compounds **9–11** to a pH 5.5 buffer system (KH_2PO_4/Na_2HPO_4 according to European Pharmacopoea) at 37 °C. Even after 6 h NMR analysis did not show any signs of decomposition.

Strangely enough, mesylates (e.g., **3** or corresponding dimethylaminoethyl containing compound **24**) do not show antiproliferative activity in our hands. However, the chemical stability of mesylates under (aqueous) assay conditions (48 h incubation before read out) should be considered before mesylates are regarded as inactive.

Relating linker chain lengths to antiproliferative activity reveal a clear trend to shorter chains, but differ from series to series (Table 3).

In conclusion, series of new 6-azanaphthoquinone pyrrolo-annelated compounds containing various linkers to alkylating groups (oxiranyl, aziridinyl, mesylate) and/or dimethylaminoalkyl groups have been synthesized and analytically characterized.[11] The resulting compounds were tested for antiproliferative activity against different cell lines. Exchange of amino groups (from inactive compounds) to oxiranyl and aziridinyl groups led to antiproliferative activity, which could be explained by an alkylating mechanism of action. Oxirane **9** showed remarkable activity, and series of aziridinyl derivatives including compounds **7** and **32** cover an activity range from very good to moderate. For the aziridine series, C4 linker chains revealed the highest activity. These studies provide useful information for further studies and for the development of an extended compound library.

Table 3
SAR for linker chain lengths within compound series containing alkylating groups

	Series	Optimum
Key structure **1**[e]		
Oxirane deriv.	9 (C1)–10 (C3)–11 (C6)	9 (C1)
Aziridin deriv.	6 (C2)–7 (C4)–8 (C7)	7 (C4)
OH-aziridin deriv.	12 (C2)–13 (C3)–14 (C6)	12 (C2)
Key structure **2**[e]		
Aziridin deriv.	31 (C2)–32 (C4)–33 (C7)	32 (C4)

[e] Key structure **1** (pyrrole ring unsubstituted) and **2** (pyrrole ring substituted by dimethylaminoethyl) refer to Figure 1. Column 'Series' denotes a compound according to Table 1 and its chain length given in round brackets. Column 'Optimum' denotes the best chain length within the series.

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10. The XTT assay[9] quantifies cellular metabolic activity which correlates with cellular viability and/or cell number. This cytotoxicity assessment has been conducted with five diverse tumor cell lines, namely KB/HeLa (ATCC CCL17, human cervix carcinoma), SKOV3 (ATCC HTB-77, human ovarian carcinoma), SF268 (NCI 503138, CNS cancer glioma), NCI-H460 (NCI 503473, large cell lung cancer) and RKOp27 (human colon adenocarcinoma). For the assay the cells are seeded on 96 well MTPs (Greiner) with an Eppendorf Multipette with a 2.5 ml Combitip as described below:

Cell line	Number per well	Volume (μl) per well	Media
KB/ HeLa	2500	125	RPMI 1640 + 10% FCSi + 2% PSG
SKOV3	3750	125	RPMI 1640 + 10% FCSi + 2% PSG
SF268	5000	125	RPMI 1640 + 10% FCSi + 2% PSG
NCI-H460	1000	125	RPMI 1640 + 10% FCSi + 2% PSG
RKOp27	6250	125	DMEM + 10% FCSi + 2% PSG + 1% Hepes

Test compounds in 100% DMSO are added to the tumor cell lines in a 10 point dose response starting at 31.6 μg/ml with halflog dilution steps and adjustment of the final DMSO concentrations to 0.3%. After 45 h of incubation at 37 °C/ 5%CO_2 1 mg/ml XTT (Serva, cat. no 38450) and 76.6 μg/ml PMS (Sigma, cat. no P9625) are incubated with the cells for additional 3 h. After 48 h of total compound incubation cellular metabolic activity is quantified by single point measurement of absorbance at 490 nm. Non-treated cells and blank controls w/o cells are set as reference values of 0% and 100% inhibition, respectively. EC50 determination was carried out employing the regression software GraphPad Prism™.

11. All of the final structures were confirmed by ^{1}H NMR, ^{13}C NMR, IR, and MS as the following.

Compound **2a**: Mp = 212 °C. ^{1}H NMR (DMSO): δ (ppm): 2.17 (s, 6H), 2.47–2.50 (m, 2H), 2.78–2.93 (m, 2H), 7.15 (s, 1H), 7.79 (d, J = 4.9 Hz, 1H), 7.89 (d, J = 4.9 Hz, 1H), 8.91 (d, J = 4.9 Hz, 1H), 9.09 (s, 1H). ^{13}C NMR (DMSO): δ (ppm): 23.8, 45.0, 59.4, 118.5, 124.7, 126.0, 127.3, 132.9, 136.6, 140.5, 147.0, 154.3, 174.4, 179.2. IR (KBr): ν_{max} 3424, 2924, 2834, 1661, 1585, 1512, 1473, 1433, 1421, 1392, 1340, 1314, 1274, 1249, 1224, 917, 736 cm^{-1}. MS: m/z (% relative intensity) 269 (M^+, 1), 254 (8), 211 (7), 111 (6), 97 (10), 83 (11), 71 (16), 58 (100), 43 (22).

Compound **2b**: Mp = 173 °C. ^{1}H NMR (DMSO): δ (ppm): 1.69 (m, 2H), 2.11 (s, 6H), 2.23 (t, J = 6.9, 2H), 2.70 (t, J = 7.3, 2H), 7.20 (s, 1H), 7.83 (d, J = 4.5 Hz, 1H), 8.99 (d, J = 4.9 Hz, 1H), 9.12 (s, 1H). ^{13}C NMR (DMSO): δ (ppm): 23.2, 27.3, 45.2, 58.8, 118.7, 123.8, 126.1, 126.6, 127.1, 132.1, 139.6, 147.1, 155.1, 174.0, 178.0. IR (KBr): ν_{max} 3426, 3079, 2938, 2756, 1653, 1586, 1393, 1220 cm^{-1}. MS: m/z (% relative intensity) 283 (M^+, 3), 223 (1), 212 (4), 84 (1), 78 (2), 58 (100), 42 (8).

Compound **3**: Mp = 164 °C. ^{1}H NMR (DMSO): δ (ppm): 3.10 (s, 3H), 4.59 (t, J = 4.8 Hz, 2H), 6.72 (d, J = 2.8 Hz, 1H), 7.51 (d, J = 2.8 Hz, 1H), 7.82 (d, J = 5.0 Hz, 1H), 8.99 (d, J = 5.0 Hz, 1H), 9.15 (s, 1H). ^{13}C NMR (DMSO): δ (ppm): 36.6, 47.8, 68.7, 107.6, 118.5, 126.3, 128.3, 129.4, 133.6, 138.6, 147.5, 155.2, 174.8, 179.2. IR (KBr): ν_{max} 1671, 1657, 1593, 1502, 1392, 1339, 1176 cm^{-1}. MS: m/z (% relative intensity) 320 (M^+, 9), 241 (27), 223 (21), 97 (28), 83 (1), 69 (63), 57 (100).

Compound **4**: Mp = 151 °C. ^{1}H NMR (DMSO): δ (ppm): 1.69 (m, 2H), 1.87 (m, 2H), 3.15 (s, 3H), 4.21 (t, J = 6.0 Hz, 2H), 4.45 (t, J = 6.8 Hz, 2H), 7.00 (d, J = 2.8 Hz, 1H), 7.52 (d, J = 2.8 Hz, 1H), 7.81 (d, J = 4.9 Hz, 1H), 8.98 (d, J = 4.9 Hz, 1H), 9.14 (s, 1H). ^{13}C NMR (DMSO): δ (ppm): 25.6, 26.5, 36.5, 48.1, 69.9, 107.6, 118.4, 126.4, 128.0, 129.3, 133.0, 138.6, 147.5, 155.1, 174.5, 179.1. IR (KBr): ν_{max} 1671, 1661, 1586, 1502, 1342, 1247, 1173 cm^{-1}. MS: m/z (% relative intensity) 348 (M^+, 86), 252 (100), 225 (72), 223 (87), 211 (80), 170 (53), 55 (91). Anal. Calcd for $C_{16}H_{16}N_2O_5S$: C, 55.15; H, 4.63; N, 8.04. Found: C, 55.42; H, 4.77; N, 7.97.

Compound **5**: Mp = 92 °C. ^{1}H NMR ($CDCl_3$): δ (ppm): 1.34 (m, 6H), 1.76 (m, 4H), 3.00 (s, 3H), 4.17 (t, J = 6.4 Hz, 2H), 4.40 (t, J = 7.3 Hz, 2H), 6.71 (d, J = 2.8 Hz, 1H), 6.99 (d, J = 2.8 Hz, 1H), 7.88 (d, J = 5.0 Hz, 1H), 8.93 (d, J = 5.0 Hz, 1H), 9.29 (s, 1H). ^{13}C NMR ($CDCl_3$): δ (ppm): 37.2, 49.4, 69.8, 108.1, 118.6, 126.6, 128.6, 129.6, 131.4, 139.0, 148.3, 154.8, 175.1, 179.4. IR (KBr): ν_{max} 1664, 1586, 1498, 1346, 1243, 1162 cm^{-1}. MS: m/z (% relative intensity) 390 (M^+, 10), 225 (13), 211 (21), 198 (25), 149 (51), 69 (83), 57 (100). Anal. Calcd for $C_{19}H_{22}N_2O_5S$: C, 58.45; H, 5.68; N, 7.17. Found: C, 58.19; H, 5.81; N, 6.97.

Compound **6**: Mp = 174 °C. ^{1}H NMR ($CDCl_3$): δ (ppm): 1.06 (m, 2H), 1.69 (m, 2H), 2.46 (t, J = 5.8 Hz, 2H), 4.63 (t, J = 5.8 Hz, 2H), 6.77 (d, J = 2.8 Hz, 1H), 7.15 (d, J = 2.8 Hz, 1H), 7.92 (d, J = 4.9 Hz, 1H), 8.92 (d, J = 4.9 Hz, 1H), 9.33 (s, 1H). ^{13}C NMR ($CDCl_3$): δ (ppm): 27.1, 49.8, 60.9, 118.8, 126.6, 128.9, 129.6, 132.6, 139.2, 148.4, 154.9, 175.3, 179.6. IR (KBr): ν_{max} 1664, 1650, 1586, 1502, 1374, 1247 cm^{-1}. MS: m/z (% relative intensity) 267 (M^+, 7), 239 (M^+−28, 8), 222 (8), 211 (10), 79 (7), 45 (100). Anal. Calcd for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.47; H, 5.12; N, 15.44.

Compound **7**: Mp = 74–75 °C. ^{1}H NMR ($CDCl_3$): δ (ppm): 1.01 (m, 2H), 1.51–1.64 (m, 4H), 1.90 (m, 2H), 2.16 (t, J = 6.9 Hz, 2H), 4.42 (t, J = 7.2 Hz, 2H), 6.68 (d, J = 2.8 Hz, 1H), 6.98 (d, J = 2.8 Hz, 1H), 7.84 (d, J = 5.0 Hz, 1H), 8.90 (d, J = 5.0 Hz, 1H), 9.26 (s, 1H). ^{13}C NMR ($CDCl_3$): δ (ppm): 26.6, 27.1, 28.8, 49.4, 61.0, 108.0, 118.6, 126.6, 128.5, 129.6, 131.3, 139.0, 148.3, 154.7, 175.1, 179.4. IR (KBr): ν_{max} 1675, 1657, 1590, 1388, 1251, 1197 cm^{-1}. MS: m/z (% relative intensity) 295 (M^+, 7), 252 (24), 225 (12), 221 (18), 97 (37), 69 (41), 56 (100). Anal. Calcd for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23. Found: C, 69.05; H, 5.95; N, 14.17.

Compound **8**: Mp = 94 °C. ^{1}H NMR ($CDCl_3$): δ (ppm): 0.98 (m, 2H), 1.31 (m, 6H), 1.47 (m, 2H), 1.62 (m, 2H), 1.80 (m, 2H), 2.09 (t, J = 6.8 Hz, 2H), 4.38 (t, J = 7.3 Hz, 2H), 6.69 (d, J = 2.8 Hz, 1H), 6.96 (d, J = 2.8 Hz, 1H), 7.86 (d, J = 4.9 Hz, 1H), 8.92 (d, J = 4.9 Hz, 1H), 9.29 (s, 1H). ^{13}C NMR ($CDCl_3$): δ (ppm): 26.3, 27.0, 27.1, 29.0, 29.5, 30.8, 49.6, 61.8, 108.0, 118.6, 126.6, 128.5, 129.6, 131.3, 139.0, 148.3, 154.7, 175.1, 179.4. IR (KBr): ν_{max} 1657, 1586, 1498, 1371, 1243 cm^{-1}. MS: m/z (% relative intensity) 337 (M^+, 18), 266 (11), 200 (14), 98 (14), 71 (15), 57 (62), 56 (100). Anal. Calcd for $C_{20}H_{23}N_3O_2$: C, 71.19; H, 6.87; N, 12.45. Found: C, 70.94; H, 6.98; N, 12.21.

Compound **9**: Mp = 128 °C. ^{1}H NMR ($CDCl_3$): δ (ppm): 2.57 (dd, J = 2.5 Hz, 4.8 Hz, 1H), 2.90 (m, 1H), 3.41 (m, 1H), 4.29 (dd, J = 6.3 Hz, 14.5 Hz, 1H), 5.13 (dd, J = 2.5 Hz, 14.5 Hz, 1H), 6.80 (d, J = 2.8 Hz, 1H), 7.11 (d, J = 2.8 Hz, 1H), 7.95 (dd, J = 0.8 Hz, 5.0 Hz, 1H), 9.00 (d, J = 5.0 Hz, 1H), 9.36 (d, J = 0.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ (ppm): 45.4, 50.6, 50.8, 108.6, 118.9, 126.6, 128.5, 128.9, 132.3, 139.2, 148.4, 155.1, 175.7, 179.6. IR (KBr): ν_{max} 1677, 1652, 1586, 1498, 1374, 1251 cm^{-1}. MS: m/z (% relative intensity) 254 (M^+, 16), 212 (87), 211 (81), 155 (29), 77 (42), 51 (78), 50 (100). Anal. Calcd for $C_{14}H_{10}N_2O_3 \cdot 0.2\ H_2O$: C, 65.21; H, 4.07; N, 10.86. Found: C, 65.37; H, 4.35; N, 10.80.

Compound **10**: Mp = 103–104 °C. ^{1}H NMR ($CDCl_3$): δ (ppm): 1.34 (m, 1H), 1.65 (m, 1H), 1.91 (m, 2H), 2.36 (dd, J = 2.7 Hz, 4.9 Hz, 1H), 2.63 (m, 1H), 2.83 (m, 1H), 4.36 (m, 1H), 6.56 (d, J = 2.8 Hz, 1H), 6.95 (d, J = 2.8 Hz, 1H), 7.73 (d, J = 5.0 Hz, 1H), 8.81 (d, J = 5.0 Hz, 1H), 9.13 (s, 1H). ^{13}C NMR ($CDCl_3$): δ (ppm): 27.3, 28.8, 46.3, 48.7, 51.3, 107.8, 118.3, 126.3, 128.4, 129.3, 131.4, 138.7, 148.0, 154.5, 174.7, 179.0. IR (KBr): ν_{max} 1675, 1654, 1586, 1498, 1374, 1247 cm^{-1}. MS: m/z (% relative intensity) 282 (M^+, 10), 223 (28), 211 (38), 198 (35), 170 (24), 69 (100), 55 (71). Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.08; H, 5.00; N, 9.92. Found: C, 68.03; H, 5.24; N, 9.74.

Compound **11**: Mp = 53–55 °C. ^{1}H NMR ($CDCl_3$): δ (ppm): 1.37 (m, 8H), 1.82 (m, 2H), 2.40 (dd, J = 2.8 Hz, 5.0 Hz, 1H), 2.68 (m, 1H), 2.83 (m, 1H), 4.40 (t, J = 7.3 Hz, 2H), 6.71 (d, J = 2.8 Hz, 1H), 6.98 (d, J = 2.8 Hz, 1H), 7.88 (dd, J = 0.8 Hz, 4.9 Hz, 1H), 8.93 (d, J = 4.9 Hz, 1H), 9.30 (s, 1H). ^{13}C NMR ($CDCl_3$): δ (ppm): 25.7, 26.3, 28.8, 30.7, 32.2, 46.9, 49.5, 52.1, 108.1, 118.6, 126.7, 128.6, 129.7, 131.3, 139.1, 148.3, 154.8, 175.1, 179.5. IR (KBr): ν_{max} 1661, 1586, 1498, 1374, 1247 cm^{-1}. MS: m/z (% relative intensity) 324 (M^+, 23), 293 (14), 225 (24), 212 (69), 211 (100), 199 (24), 55 (91). Anal. Calcd for $C_{19}H_{20}N_2O_3 \cdot 0.2\ H_2O$: C, 69.58; H, 6.27; N, 8.54. Found: C, 69.60; H, 6.44; N, 8.26.

Compound **12**: Mp = 181 °C. ^{1}H NMR (DMSO): δ (ppm): 1.16 (m, 2H), 1.63 (m, 2H), 2.17 (dd, J = 6.0 Hz, 12.0 Hz, 1H), 2.34 (dd, J = 5.3 Hz, 12.0 Hz, 1H), 3.97 (m, 1H), 4.24 (dd, J = 8.8 Hz, 13.3 Hz, 1H), 4.77 (dd, J = 3.3 Hz, 13.3 Hz, 1H), 5.04 (d, J = 5.5 Hz, 1H), 6.70 (d, J = 2.8 Hz, 1H), 7.43 (d, J = 2.8 Hz, 1H), 7.85 (d, J = 5.0 Hz, 1H), 9.01 (d, J = 5.0 Hz, 1H), 9.18 (s, 1H). ^{13}C NMR (DMSO): δ (ppm): 26.5, 26.7, 53.3, 64.9, 69.5, 107.2, 118.5, 126.5, 128.1, 129.5, 134.2, 138.6, 147.6, 155.1, 174.6, 179.2. IR (KBr): ν_{max} 3117, 1673, 1652, 1498, 1385, 1249 cm^{-1}. MS: m/z (% relative intensity) 297 (M^+, 1), 269 (10), 212 (9), 211 (7), 57 (17), 56 (100).

13 ^{1}H NMR ($CDCl_3$): δ (ppm): 1.18 (m, 2H), 1.47 (m, 2H), 1.74 (m, 2H), 2.01 (m, 4H), 2.47 (dd, J = 8.5 Hz, 11.8 Hz, 1H), 3.78 (m, 1H), 4.47 (t, J = 7.3 Hz, 2H), 6.74 (d, J = 2.8 Hz, 1H), 7.03 (d, J = 2.8 Hz, 1H), 7.90 (d, J = 5.0 Hz, 1H), 8.95 (d, J = 5.0 Hz, 1H), 9.32 (s, 1H). ^{13}C NMR ($CDCl_3$): δ (ppm): 26.9, 27.3, 27.5, 31.3, 49.5, 67.3, 70.1, 108.2, 118.7, 126.7, 128.7, 129.7, 131.6, 139.1, 148.4, 154.8, 175.2, 179.5. IR (KBr): ν_{max} 3397, 1671, 1657, 1586, 1500, 1374, 1229 cm^{-1}. MS: m/z (% relative intensity) 325 (M^+, 1), 269 (M^+−56, 1), 211 (3), 199 (2), 126 (3), 57 (16), 56 (100). Anal. Calcd for $C_{18}H_{19}N_3O_3$: C, 66.45; H, 5.89; N, 12.91. Found: C, 63.30; H, 5.80; N, 12.02.

Compound **14**: Mp = 97 °C. ^{1}H NMR ($CDCl_3$): δ (ppm): 1.10 (m, 1H), 1.33 (m, 9H), 1.75 (m, 5H), 2.41 (dd, J = 8.7 Hz, 11.9 Hz, 1H), 3.16 (br s, 1H), 3.67 (m, 1H), 4.40 (t, J = 7.3 Hz, 2H), 6.72 (d, J = 2.5 Hz, 1H), 7.12 (d, J = 2.8 Hz, 1H), 7.89 (dd, J = 0.6 Hz, 4.9 Hz, 1H), 8.94 (d, J = 4.9 Hz, 1H), 9.31 (d, J = 0.6 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ (ppm): 25.3, 26.3, 26.8, 27.4, 29.0, 30.8, 34.5, 49.6, 67.4, 70.5, 108.1, 118.7, 126.7, 128.6, 129.7, 131.4, 139.1, 148.4, 154.8, 175.1, 179.5. IR (KBr): ν_{max} 3390, 1657, 1586, 1498, 1378, 1247 cm^{-1}. MS: m/z (% relative intensity) 367 (M^+, 6), 311 (M^+−56, 7), 211 (17), 199 (11), 83 (96), 69 (56), 56 (100). Anal. Calcd for $C_{21}H_{25}N_3O_3 \cdot 0.3\ H_2O$: C, 67.65; H, 6.92; N, 11.27. Found: C, 67.60; H, 6.99; N, 11.06.

Compound **15**: Mp = 145 °C. ^{1}H NMR ($CDCl_3$): δ (ppm): 0.99 (s, 9H), 4.04 (d, J = 4.8 Hz, 2H), 4.56 (t, J = 4.8 Hz, 2H), 6.74 (d, J = 2.8 Hz, 1H), 7.09 (d, J = 2.8 Hz, 1H), 7.22 (m, 6H), 7.42 (m, 4H), 7.95 (d, J = 4.9 Hz, 1H), 8.99 (d, J = 4.9 Hz, 1H), 9.24 (s, 1H). ^{13}C NMR ($CDCl_3$): δ (ppm): 18.9, 26.8, 51.9, 62.4, 107.6, 118.6, 126.6, 127.6, 129.0, 129.4, 129.6, 132.5, 133.2, 133.4, 139.2, 148.3, 154.8, 175.1, 179.6. IR (KBr): ν_{max} 1671, 1657, 1590, 1505, 1381, 1254, 1106, 710 cm^{-1}. MS: m/z (% relative intensity) 423 (M^+−57, 3), 199 (6), 149 (13), 86 (77), 84 (100), 77 (21), 69 (78).

Compound **16**: ^{1}H NMR ($CDCl_3$): δ (ppm): 1.03 (s, 9H), 1.59 (m, 2H), 1.98 (m, 2H), 3.71 (t, J = 6.1 Hz, 2H), 4.45 (t, J = 7.0 Hz, 2H), 6.75 (d, J = 2.8 Hz, 1H), 6.95 (d, J = 2.8 Hz, 1H), 7.38 (m, 6H), 7.66 (m, 4H), 7.92 (dd, J = 0.6 Hz, 5.0 Hz, 1H), 8.96 (d, J = 5.0 Hz, 1H), 9.35 (d, J = 0.6 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ (ppm): 19.0, 26.7, 27.3, 29.2, 49.3, 63.0, 108.0, 118.6, 126.6, 127.5, 128.6, 129.5, 129.7,

131.3, 135.4, 139.0, 148.3, 154.7, 175.0, 179.4. IR (KBr): ν_{max} 1671, 1657, 1586, 1502, 1247, 1109 cm^{-1}. MS: *m*/*z* (% relative intensity) 453 (13), 452 (42), 451 (M^+−57, 100), 395 (8), 253 (9), 199 (9), 183 (14), 77 (7).

Compound **17**: ^{1}H NMR ($CDCl_3$): δ (ppm): 1.04 (s, 9H), 1.34 (m, 6H), 1.56 (m, 2H), 1.84 (m, 2H), 3.66 (t, *J* = 6.4 Hz, 2H), 4.42 (t, *J* = 7.3 Hz, 2H), 6.76 (d, *J* = 2.8 Hz, 1H), 6.98 (d, *J* = 2.8 Hz, 1H), 7.36 (m, 6H), 7.67 (m, 4H), 7.93 (dd, *J* = 0.8 Hz, 5.0 Hz, 1H), 8.97 (d, *J* = 5.0 Hz, 1H), 9.37 (d, *J* = 0.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ (ppm): 19.1, 25.5, 26.4, 26.8, 28.7, 30.8, 32.3, 49.6, 63.7, 108.0, 118.6, 126.7, 127.5, 128.6, 129.4, 129.7, 131.3, 133.9, 135.4, 139.1, 148.4, 154.8, 175.1, 179.5. IR (KBr): ν_{max} 1671, 1657, 1586, 1505, 1378, 1247, 1109 cm^{-1}. MS: *m*/*z* (% relative intensity) 453 (12), 494 (37), 493 (100), 199 (56), 183 (22), 181 (17), 77 (31).

Compound **18**: Mp = 163 °C. ^{1}H NMR (DMSO-d_6): δ (ppm): 3.73 (m, 2H), 4.45 (t, *J* = 5.5 Hz, 2H), 4.96 (t, *J* = 5.4 Hz, 1H), 6.65 (d, *J* = 2.8 Hz, 1H), 7.41 (d, *J* = 2.8 Hz, 1H), 7.79 (d, *J* = 5.0 Hz, 1H), 8.96 (d, *J* = 5.0 Hz, 1H), 9.10 (s, 1H). ^{13}C NMR ($CDCl_3$): δ (ppm): 51.3, 60.1, 107.2, 118.4, 126.3, 128.0, 129.2, 133.8, 138.5, 147.5, 155.1, 174.5, 179.1. IR (KBr): ν_{max} 3227, 1657, 1646, 1593, 1502, 1374, 1251, 1070 cm^{-1}. MS: *m*/*z* (% relative intensity) 242 (M^+, 15), 241 (100), 222 (32), 210 (63), 198 (36), 169 (51), 78 (39).

Compound **19**: Mp = 160 °C. ^{1}H NMR (DMSO-d_6): δ (ppm): 1.40 (m, 2H), 1.78 (m, 2H), 3.40 (m, 2H), 4.43 (m, 3H), 6.69 (d, *J* = 2.8 Hz, 1H), 7.50 (d, *J* = 2.8 Hz, 1H), 7.81 (d, *J* = 5.0 Hz, 1H), 8.98 (d, *J* = 5.0 Hz, 1H), 9.14 (s, 1H). ^{13}C NMR (DMSO-d_6): δ (ppm): 27.2, 29.4, 48.7, 60.3, 107.5, 118.4, 126.4, 128.0, 129.2, 133.0, 138.6, 147.5, 155.1, 174.4, 179.1. IR (KBr): ν_{max} 3262, 1668, 1657, 1590, 1498, 1374, 1247 cm^{-1}. MS: *m*/*z* (% relative intensity) 270 (M^+, 100), 252 (M^+−18, 27), 225 (32), 213 (36), 211 (40), 199 (31), 170 (39).

Compound **20**: Mp = 69 °C. ^{1}H NMR ($CDCl_3$): δ (ppm): 1.33 (m, 6H), 1.51 (m, 2H), 1.81 (m, 2H), 2.23 (s, 1H), 3.58 (t, *J* = 6.4 Hz, 2H), 4.39 (t, *J* = 7.3 Hz, 2H), 6.71 (d, *J* = 2.8 Hz, 1H), 6.98 (d, *J* = 2.76 Hz, 1H), 7.88 (dd, *J* = 0.8 Hz, 5.0 Hz, 1H), 8.92 (d, *J* = 5.0 Hz, 1H), 9.28 (s, 1H). ^{13}C NMR ($CDCl_3$): δ (ppm): 25.5, 26.4, 28.8, 30.7, 32.5, 49.6, 62.5, 108.1, 118.7, 126.7, 128.6, 129.6, 131.4, 139.1, 148.2, 154.7, 175.0, 179.5. IR (KBr): ν_{max} 3362, 1675, 1650, 1586, 1498, 1388, 1251 cm^{-1}. MS: *m*/*z* (% relative intensity) 200 (39), 199 (100), 181 (11), 139 (9), 88 (35), 77 (31), 55 (28).

Compound **21**: Mp = 154 °C. ^{1}H NMR ($CDCl_3$): δ (ppm): 2.18 (s, 6H), 2.45 (t, *J* = 7.2 Hz, 2H), 2.86 (t, *J* = 7.2 Hz, 2H), 3.72 (t, *J* = 5.4 Hz, 2H), 4.43 (t, *J* = 5.4 Hz, 2H), 5.04 (s, 1H), 7.31 (s, 1H), 7.82 (d, *J* = 4.9 Hz, 1H), 8.99 (d, *J* = 4.9 Hz, 1H), 9.13 (s, 1H). ^{13}C NMR ($CDCl_3$): δ (ppm): 23.2, 45.0, 51.2, 58.9, 60.1, 118.4, 123.9, 124.9, 126.4, 129.0, 132.5, 138.9, 147.4, 155.0, 174.9, 179.9. IR (KBr): ν_{max} 3419, 2820, 1664, 1642, 1584, 1490, 1465, 1395, 1263, 1221, 1068, 933 cm^{-1}. MS: *m*/*z* (% relative intensity) 313 (M^+, 1), 269 (1), 211 (3), 155 (1), 128 (2), 101 (2), 91 (3), 78 (4), 58 (100).

Compound **22**: ^{1}H NMR ($CDCl_3$): δ (ppm): 1.54–1.67 (m, 2H), 1.86–1.97 (m, 2H), 2.29 (s, 6H), 2.56 (t, *J* = 7.5 Hz, 2H), 2.98 (t, *J* = 7.4 Hz, 2H), 3.23 (s, 1H), 3.65 (t, *J* = 6.3 Hz, 2H), 4.42 (t, *J* = 7.3 Hz, 2H), 6.92 (s, 1H), 7.87 (dd, *J* = 4.9 Hz, 0.7 Hz, 1H), 8.92 (d, *J* = 4.9 Hz, 1H), 9.28 (s, 1H). ^{13}C NMR ($CDCl_3$): δ (ppm): 23.6, 27.3, 29.3, 45.1, 49.2, 59.1, 61.6, 118.6, 125.1, 125.5, 126.7, 129.7, 130.4, 139.5, 148.2, 154.7, 175.0, 180.2. IR (KBr): ν_{max} 3378, 2940, 1653, 1585, 1493, 1395, 1261, 1059, 935, 734, 688 cm^{-1}. MS: *m*/*z* (% relative intensity) 341 (M^+, 2), 326 (2), 223 (1), 128 (1), 101 (1), 83 (1), 69 (1), 58 (100).

Compound **23**: ^{1}H NMR ($CDCl_3$): δ (ppm): 1.37 (s, 6H), 1.54 (t, *J* = 6.1 Hz, 2H), 1.83 (t, *J* = 6.1 Hz, 2H), 2.06 (s, 1H), 2.30 (s, 6H), 2.57 (t, *J* = 7.2 Hz, 2H), 3.01 (t, *J* = 7.4 Hz, 2H), 3.61 (t, *J* = 6.4 Hz, 2H), 4.39 (t, *J* = 7.3 Hz, 2H), 6.90 (s, 1H), 7.91 (d, *J* = 4.9 Hz, 1H), 8.95 (d, *J* = 5.0 Hz, 1H), 9.33 (s, 1H). ^{13}C NMR ($CDCl_3$): δ (ppm): 23.7, 25.6, 26.5, 28.8, 30.7, 45.3, 49.5, 59.2, 62.7, 118.6, 125.2, 125.5, 126.8, 129.8, 130.3, 139.6, 148.3, 154.7 175.0, 180.4. IR (KBr): ν_{max} 3384, 2931, 1653, 1585, 1492, 1465, 1419, 1395, 1261, 1054, 934 cm^{-1}. MS: *m*/*z* (% relative intensity) 383 (M^+, 2), 368 (12), 325 (1), 254 (1), 237 (1), 225 (2), 211 (6), 141 (1), 128 (1), 97 (1), 58 (100).

Compound **24**: ^{1}H NMR ($CDCl_3$): δ (ppm): 2.32 (s, 6H), 2.62 (t, *J* = 7.2 Hz, 2H), 2.95 (s, 3H), 3.03 (t, *J* = 7.2 Hz, 2H), 4.60 (t, *J* = 4.9 Hz, 2H), 4.74 (t, *J* = 4.7 Hz, 2H), 7.02 (s, 1H), 7.91 (d, *J* = 4.9 Hz, 1H), 8.98 (d, *J* = 5.1 Hz, 1H), 9.31 (s, 1H). ^{13}C NMR ($CDCl_3$): δ (ppm): 23.4, 37.4, 45.1, 48.7, 58.8, 67.8, 118.7, 125.2, 126.2, 126.4, 129.5, 131.7, 139.5, 148.2, 155.1, 175.4, 180.3. IR (KBr): ν_{max} 3424, 2927, 2856, 1663, 1585, 1495, 1464, 1420, 1396, 1352, 1266, 1174, 1009, 916, 803 cm^{-1}. MS: *m*/*z* (% relative intensity) 391 (M^+, 1), 195 (3), 165 (3), 125 (9), 111 (16), 97 (30), 84 (49), 58 (100).

Compounds **25**, **26**: Due to instability, these *Compounds* were used immediately for the next step without spectroscopic characterization.

Compound **27**: ^{1}H NMR ($CDCl_3$): δ (ppm): 2.28 (s, 12H), 2.52 (t, *J* = 7.2 Hz, 2H), 2.70 (t, *J* = 6.6 Hz, 2H), 2.99 (t, *J* = 7.3 Hz, 2H), 4.50 (t, *J* = 6.4 Hz, 2H), 6.95 (s, 1H), 7.89 (d, *J* = 4.9 Hz, 1H), 8.94 (d, *J* = 5.0 Hz, 1H), 9.31 (s, 1H). ^{13}C NMR ($CDCl_3$): δ (ppm): 23.7, 45.3, 45.6, 47.2, 59.1, 59.4, 118.6, 125.2, 125.5, 126.7, 129.7, 130.8, 139.5, 148.2, 154.7, 175.1, 180.3. IR (KBr): ν_{max} 3415, 2929, 2823, 2778, 1653, 1584, 1493, 1465, 1420, 1396, 1265, 1174, 1042, 934 cm^{-1}. MS: *m*/*z* (% relative intensity) 326 (M^+, 2), 240 (7), 212 (4), 97 (4), 83 (4), 71 (6), 58 (100), 44 (40), 30 (20).

Compound **28**: ^{1}H NMR ($CDCl_3$): δ (ppm): 1.92–2.03 (m, 2H), 2.20–2.30 (m, 14H), 2.56 (t, *J* = 7.6 Hz, 5.0 Hz, 2H), 2.99 (t, *J* = 7.2 Hz, 2H), 4.43 (t, *J* = 6.7 Hz, 2H), 6.94 (s, 1H), 7.89 (d, *J* = 4.9 Hz, 1H), 8.94 (d, *J* = 4.9 Hz, 1H), 9.31 (s, 1H). ^{13}C NMR ($CDCl_3$): δ (ppm): 23.7, 28.4, 45.3, 45.5, 47.3, 55.8, 59.2, 118.6, 125.0, 125.5, 126.8, 129.7, 131.0, 139.6, 148.3, 154.7, 174.9, 180.3. IR (KBr): ν_{max} 3429, 2937, 2765, 1652, 1583, 1490, 1394, 1259, 933, 734 cm^{-1}. MS: *m*/*z* (% relative intensity) 354 (M^+, 1), 254 (2), 149 (5), 111 (4), 97 (7), 85 (10), 71 (14), 58 (100).

Compound **29**: ^{1}H NMR ($CDCl_3$): δ (ppm): 2.30 (s, 6H), 2.32 (s, 1H), 2.45 (s, 3H), 2.58 (t, *J* = 7.6 Hz, 2H), 2.98–3.05 (m, 4H), 4.53 (t, *J* = 5.8 Hz, 2H), 6.96 (s, 1H), 7.91 (d, *J* = 4.4 Hz, 1H), 8.97 (d, *J* = 4.9 Hz, 1H), 9.34 (s, 1H). ^{13}C NMR ($CDCl_3$): δ (ppm): 23.8, 36.3, 45.3, 49.2, 51.8, 59.1, 118.6, 125.3, 125.7, 126.7, 129.9, 130.9, 139.6, 148.3, 154.8, 175.2, 180.4. IR (KBr): ν_{max} 3415, 2926, 2854, 1653, 1584, 1492, 1465, 1419, 1395, 1263, 933 cm^{-1}. MS: *m*/*z* (% relative intensity) 326 (M^+, 2), 240 (7), 212 (4), 97 (4), 83 (4), 71 (6), 58 (100), 44 (40).

Compound **30**: ^{1}H NMR ($CDCl_3$): δ (ppm): 2.28–2.33 (m, 8H), 2.59 (t, *J* = 7.1 Hz, 2H), 2.72–2.83 (m, 2H), 3.00 (t, *J* = 7.0 Hz, 2H), 3.10 (t, *J* = 5.9 Hz, 2H), 3.57 (t, *J* = 4.9 Hz, 2H), 4.52 (t, *J* = 5.9 Hz, 2H), 6.99 (s, 1H), 7.91 (d, *J* = 5.1 Hz, 1H), 8.96 (d, *J* = 4.7 Hz, 1H), 9.32 (s, 1H). ^{13}C NMR ($CDCl_3$): δ (ppm): 23.7, 45.3, 49.1, 49.7, 50.9, 59.1, 60.9, 118.7, 125.2, 125.7, 126.7, 129.8, 131.2, 139.5, 148.3, 154.8, 175.2, 180.3. IR (KBr): ν_{max} 3375, 2925, 1653, 1585, 1493, 1465, 1420, 1395, 1262, 1055, 933, 734 cm^{-1}. MS: *m*/*z* (% relative intensity) 250 (M^+, 2), 204 (2), 149 (7), 97 (8), 84 (79), 58 (100), 44 (48), 30 (22).

Compound **31**: ^{1}H NMR ($CDCl_3$): δ (ppm): 1.07 (m, 2H), 1.71 (m, 2H), 2.29 (s, 6H), 2.54–2.66 (m, 4H), 3.01 (t, *J* = 7.3 Hz 2H), 4.58 (t, *J* = 5.8 Hz, 2H), 7.04 (s, 1H), 7.91 (d, *J* = 4.9 Hz, 1H), 8.95 (d, *J* = 4.9 Hz, 1H), 9.31 (s, 1H). ^{13}C NMR ($CDCl_3$): δ (ppm): 23.7, 27.1, 45.3, 49.7, 59.2, 60.9, 118.6, 125.1, 125.8, 126.7, 129.6, 131.5, 139.6, 148.2, 154.8, 175.1, 180.4. IR (KBr): ν_{max} 3424, 2927, 1653, 1585, 1495, 1465, 1420, 1396, 1352, 1266, 1174, 1009, 916, 803, 733 cm^{-1}. MS: *m*/*z* (% relative intensity) 338 (M^+, 1), 295 (1), 211 (1), 195 (1), 149 (1), 111 (1), 97 (2), 81 (2), 69 (4), 58 (100).

Compound **32**: ^{1}H NMR ($CDCl_3$): δ (ppm): 1.02–1.05 (m, 2H), 1.49–1.61 (m, 2H), 1.65–1.67 (m, 2H), 1.83–1.98 (m, 2H), 2.15–2.22 (m, 2H), 2.26 (s, 6H), 2.52 (t, *J* = 7.5 Hz, 2H), 2.96 (t, *J* = 7.5 Hz, 2H), 4.39 (t, *J* = 7.2 Hz, 2H), 6.89 (s, 1H), 7.86 (dd, *J* = 4.9 Hz, 0.8 Hz, 1H), 8.91 (dd, *J* = 4.9 Hz, 1.9 Hz, 1H), 9.28 (s, 1H). ^{13}C NMR ($CDCl_3$): δ (ppm): 23.7, 26.7, 27.2, 28.7, 45.2, 49.3, 59.1, 61.1, 118.5, 125.2, 125.4, 126.7, 129.6, 130.2, 139.5, 148.2, 154.6, 174.9, 180.2. IR (KBr): ν_{max} 3404, 3061, 2945, 1657, 1583, 1492, 1418, 1392, 1290, 1261, 1216, 1061, 934, 903 cm^{-1}. MS: *m*/*z* (% relative intensity) 366 (M^+, 3), 323 (1), 225 (1), 211 (1), 127 (1), 98 (7), 69 (2), 58 (100).

Compound **33**: ^{1}H NMR ($CDCl_3$): δ (ppm): 1.02–1.04 (m, 2H), 1.35 (s, 6H), 1.49–1.55 (m, 2H), 1.66–1.69 (m, 2H), 1.80–1.83 (m, 2H), 2.14 (t, *J* = 6.8 Hz, 2H), 2.30 (s, 6H), 2.57 (t, *J* = 7.5 Hz, 2H), 3.01 (t, *J* = 7.5 Hz, 2H), 4.38 (t, *J* = 7.3 Hz, 2H), 6.89 (s, 1H), 7.91 (dd, *J* = 4.9 Hz, 0.8 Hz, 1H), 8.95 (d, *J* = 4.9 Hz, 1H), 9.33 (s, 1H). ^{13}C NMR ($CDCl_3$): δ (ppm): 23.8, 26.5, 27.2, 27.3, 29.1, 29.6, 30.8, 45.3, 49.6, 59.2, 61.9, 118.6, 125.2, 125.5, 126.8, 129.8, 130.3, 139.6, 148.3, 154.7, 175.0, 180.4. IR (KBr): ν_{max} 3422, 2929, 2855, 1653, 1584, 1492, 1466, 1419, 1395, 1262, 934, 734 cm^{-1}. MS: *m*/*z* (% relative intensity) 408 (M^+, 4), 363 (1), 322 (1), 225 (1), 211 (1), 127 (1), 83 (2), 69 (2), 58 (100).

Compound **34**: Mp = 97 °C. ^{1}H NMR ($CDCl_3$): δ (ppm): 1.72–1.87 (m, 2H), 1.90–2.04 (m, 2H), 2.21–2.29 (m, 16H), 2.83 (t, *J* = 7.6 Hz, 2H), 4.44 (t, *J* = 6.9 Hz, 2H), 6.87 (s, 1H), 7.90 (d, *J* = 4.9 Hz, 0.8 Hz, 1H), 8.95 (dd, *J* = 4.0 Hz, 0.9 Hz, 1H), 9.33 (s, 1H). ^{13}C NMR ($CDCl_3$): δ (ppm): 23.5, 27.7, 28.4, 47.3, 55.8, 59.3, 45.3, 45.5, 118.6, 126,8, 127.1, 129.8, 130.6, 132.9, 139.6, 148.3, 154.7, 175.0, 180.3. IR (KBr): ν_{max} 3416, 2938, 2763, 1653, 1584, 1490, 1399, 1254, 1041 cm^{-1}. MS: *m*/*z* (% relative intensity) 368 (M^+, 1), 297 (1), 226 (6), 211 (1), 149 (2), 84 (15), 72 (11), 58 (100).

Compound **35**: Mp = 94 °C. ^{1}H NMR ($CDCl_3$): δ (ppm): 1.00 (s, 9H), 2.30 (s, 6H), 2.53 (t, *J* = 7.9 Hz, 2H), 2.99 (t, *J* = 7.2 Hz, 2H), 4.04 (t, *J* = 4.9 Hz, 2H), 4.51 (t, *J* = 4.5 Hz, 2H), 7.00 (s, 1H), 7.18–7.21 (m, 6H), 7.39–7.42 (m, 4H), 7.93 (d, *J* = 4.9 Hz, 1H), 8.98 (d, *J* = 4.9 Hz, 1H), 9.21 (s, 1H). ^{13}C NMR ($CDCl_3$): δ (ppm): 19.0, 23.7, 26.8, 45.3, 51.9, 59.1, 62.5, 118.5, 124.5, 125.8, 126.7, 127.6, 129.3, 129.7, 132.2, 132.6, 135.4, 139.6, 148.2, 154.7, 174.9, 180.4. IR (KBr): ν_{max} 3418, 2927, 2854, 1663, 1652, 1583, 1491, 1464, 1425, 1390, 1265, 1110, 930, 701 cm^{-1}. MS: *m*/*z* (% relative intensity) 551 (M^+, 1), 199 (7), 167 (7), 149 (23), 97 (17), 81 (24), 69 (45), 58 (56), 44 (100).

Compound **36**: ^{1}H NMR ($CDCl_3$): δ (ppm): 1.03 (s, 9H), 1.52–1.66 (m, 2H), 1.88–2.03 (m, 2H), 2.30 (s, 6H), 2.57 (t, *J* = 7.4 Hz, 2H), 3.01 (t, *J* = 7.4 Hz, 2H), 3.70 (t, *J* = 6.0 Hz 2H), 4.41 (t, *J* = 7.1 Hz, 2H), 6.86 (s, 1H), 7.35–7.38 (m, 6H), 7.62–7.65 (m, 4H), 7.92 (d, *J* = 4.9 Hz, 1H), 8.96 (d, *J* = 5.0 Hz, 1H), 9.34 (s, 1H). ^{13}C NMR ($CDCl_3$): δ (ppm): 19.1, 23.7, 26.8, 27.4, 29.3, 45.2, 49.3, 59.2, 63.1, 118.6, 125.1, 125.5 126.8, 127.6, 129.6, 129.8, 130.2, 133.6, 135.4, 139.5, 148.3, 154.6, 174.9, 180.4. IR (KBr): ν_{max} 3416, 2928, 2854, 1667, 1653, 1585, 1493, 1396, 1262, 1111, 1086, 937, 823, 733, 704 cm^{-1}. MS: *m*/*z* (% relative intensity) 199 (100), 181 (8), 152 (3), 121 (6), 97 (2), 77 (24), 69 (4), 45 (26).

Compound **37**: ^{1}H NMR ($CDCl_3$): δ (ppm): 1.03 (s, 9H), 1.34 (m, 6H), 1.53 (m, 2H), 1.80 (m, 2H), 2.31 (s, 6H), 2.58 (t, *J* = 7.5 Hz, 2H), 3.02 (t, *J* = 6.3 Hz, 2H), 3.64 (t, *J* = 6.3 Hz 2H), 4.37 (t, *J* = 7.2 Hz, 2H), 6.89 (s, 1H), 7.32–7.38 (m, 6H), 7.62–7.67 (m, 4H), 7.91 (d, *J* = 4.9 Hz, 1H), 8.95 (d, *J* = 5.1 Hz, 1H), 9.34 (s, 1H). ^{13}C NMR ($CDCl_3$): δ (ppm): 19.1, 23.7, 25.6, 26.5, 26.8, 28.8, 30.8, 32.3, 45.2, 49.5, 59.1, 63.7, 118.5, 125.1, 125.4 126.7, 127.6, 127.5, 129.4, 129.7, 130.2, 133.9, 135.4, 139.5, 148.2, 154.6, 174.9, 180.3. IR (KBr): ν_{max} 3418, 2930, 2856, 1653, 1492, 1465, 1427, 1261, 1112, 934, 702 cm^{-1}. MS: *m*/*z* (% relative intensity) 199 (100), 181 (7), 152 (3), 137 (7), 121 (6), 97 (6), 69 (21), 45 (32).

Compound **38**: During silica gel column chromatography compound **38** decomposes to give target compound **30** in pure form.

Compound **39**: Mp = 235 °C (decomp.). ^{1}H NMR (DMSO): δ (ppm): 3.15 (t, *J* = 6.7 Hz, 2H), 3.82 (t, *J* = 7.1 Hz, 2H), 7.27 (d, *J* = 4.8 Hz, 1H), 7.78 (t, *J* = 5.3 Hz, 1H), 8.96 (d, *J* = 8.7 Hz, 1H), 9.08 (d, *J* = 5.9 Hz, 1H), 12.94 (br s, 1H). ^{13}C NMR (DMSO): δ (ppm): 28.8, 43.9, 118.6, 122.3, 123.8, 125.9, 127.5, 132.1, 139.3, 147.1, 155.2, 174.0, 180.1. ± IR (KBr): ν_{max} 1652, 1582, 1494, 1418, 1397, 1256, 1232, 1079, 927 cm^{-1}. MS: *m*/*z* (% relative intensity) 260 (M^+, 9), 224 (100), 211 (53), 196 (6), 168 (6), 156 (6), 140 (7), 128 (11), 106 (12), 78 (13).

Compound **40**: Mp = 230 °C. ^{1}H NMR (DMSO): δ (ppm): 1.97–2.11 (m, 2H), 2.85 (t, *J* = 7.1 Hz, 2H), 3.65 (t, *J* = 6.6 Hz, 2H), 7.23 (s, 1H), 7.83 (d, *J* = 4.9 Hz, 1H), 8.99 (d, *J* = 4.9 Hz, 1H), 9.13 (s, 1H), 12.91 (br s, 1H). ^{13}C NMR (DMSO): δ (ppm): 22.7, 31.9, 45.0, 118.7, 123.8, 125.3, 126.0, 126.6, 132.2, 139.5, 147.1, 155.1, 174.0, 180.0. ± IR (KBr): ν_{max} 3446, 3080, 2918, 2840, 1659, 1591, 1397, 1247, 1033, 925 cm^{-1}. MS: *m*/*z* (% relative intensity) 274 (M^+, 29), 239 (61), 225 (47), 212 (42), 211 (100), 197 (2), 183 (4), 155 (6), 140 (3), 128 (11), 106 (27), 78 (22).