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Sequential one-pot synthesis of bis(indolyl)glyoxylamides: Evaluation of antibacterial and anticancer activities

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ABSTRACT

A series of bis(indolyl)glyoxylamides **10a–n** has been designed and synthesized. In situ generated indole-3-glyoxalylchloride from the reaction of readily available indole **9** with oxalyl chloride was treated with tryptamine to produce bis(indolyl)glyoxylamides **10a–n** in 82–93% yields. All the synthesized bis(indolyl) glyoxylamides were well characterized and tested for their antibacterial activity against Gram-positive and Gram-negative bacterial strains. Compounds **10d**, **10g** and **10i** were found to display potent antibacterial activity against Gram-negative strain. Further, the cytotoxicity of bis(indolyl)glyoxylamides **10a–n** were evaluated against a panel of human cancer cell lines. Of the screened analogues, compound **10f** (IC_{50} = 22.34 μM; HeLa, 24.05 μM; PC-3, 21.13 μM; MDA-MB-231 and 29.94 μM; BxPC-3) was identified as the most potent analogue of the series. Exposure of PC-3 cells to either **10a** or **10f** resulted in increased levels of cleaved PARP1, indicating that bis(indolyl)glyoxylamides induce apoptosis in PC-3 cells. Most importantly, compounds **10d**, **10g** and **10i** were completely ineffective in mammalian cells, suggesting that they target bacterial-specific targets and thus will not display any toxicity in host cells.

Indole is a core substructure in a wide range of biologically active natural products isolated from marine organisms.[1] Particularly, diverse indole alkaloids represent an emerging class of natural products due to their biological potential as antimicrobial, anti-HIV, antipsychotic, antidepressant, antioxidant, anti-inflammatory and antitumour.[2] Among the indole alkaloids, bisindoles are a class of compounds which have received increasing attention due their diverse and profound biological activities including antimicrobial, anticancer, anti-HIV antileishmanial and anti-inflammatory.[3] Due to unique structural features and associated activities, bisindole alkaloids continue to serve as potential targets for synthetic and biomedical purposes. Literature review on bisindole scaffold reveals its wide presence in many antibacterial and anticancer lead molecules.[4] Bartik and co-workers isolated three new bisindole alkaloids namely topsentin (**1a**), bromotopsentin (**1b**) and deoxytopsentin (**1c**) from the Mediterranean sponge *Topsentia genitrix*, near Banyuls in France.[5] Topsentin (**1a**) exhibited anticancer activity (IC_{50} ~4–40 μM) towards cultured human and murine tumor cells whereas bromotopsentin (**1b**, IC_{50} = 12 μg/mL) and deoxytopsentin (**1c**, IC_{50} = 6.3 μg/mL) were found to be cytotoxic against human broncopulmonary (NSCLC-N6) cancer cells. Deoxytopsentin **1c** also showed potent antibacterial activity against various bacteria (MIC = 3.12–12.5 μg/mL).[4] Among the four bisindole alkaloids isolated by Kobayashi and co-workers from Okinawan tunicate *Rhopalaea* sp.,[6] Rhopaladin B (**2a**) exhibited inhibitory activity against cyclin dependent kinase 4 (IC_{50} = 12.5 μg/mL) and c-erbB-2 kinase (IC_{50} = 7.4 μg/mL). Rhopaladin C (**2b**) with C_6-bromo moiety was found to display activity against *Sarcina lutea* and *Corynebacterium xerosis* bacterial strains (MIC = ~16 μg/mL).[7] Hamacanthin A (**3**) containing a six-membered pyrazinone spacer unit was isolated from a deep-water marine sponge *Hamacantha* sp. and found to possess significant antimicrobial activity against *Candida albicans*, *Cryptococcus neoformans*, and *Bacillus subtilis*.[8] With a similar pyrazinone linker, in 1995 Capon and co-workers reported the isolation of dragmacidin D (**4**) from marine sponge *Spongosorites* sp. and evaluated their biological activities. Compound **4** was more active towards bacteria including *Escherichia coli* (MIC = 15.6 μg/mL); *Bacillus subtilis* (MIC = 3.1 μg/mL); *Pseudomonas aeruginosa* (MIC = 62.5 μg/mL). Also, it was more cytotoxic against P388 murine (IC_{50} = 1.4 μg/mL) and A-549 (IC_{50} = 4.5 μg/mL) human lung cancer cells (Fig. 1).[9]

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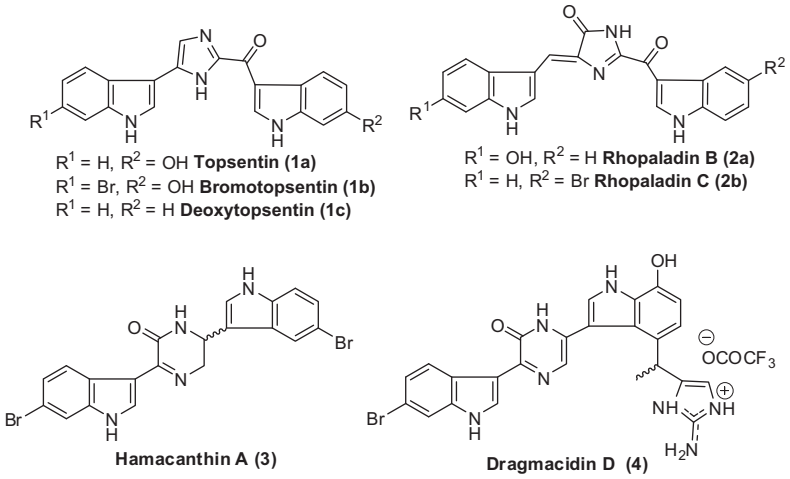
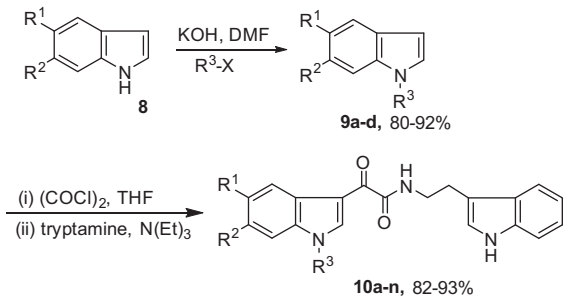


Figure 1. Representative examples of bisindole alkaloids as antibacterial and anticancer agents.

In recent past numerous bisindoles containing linear as well as cyclic linkers have been identified as antibacterial and anticancer agents (Fig. 2).[10] Kumar et al. prepared 3,2′-linked bis-indoles **5** which were found to be active against Gram-positive and Gram-negative bacteria.[11] In 2011, Singh group investigated a series of *N*-1, C-3 and C-5 trisubstituted bisindoles bearing glyoxylamide functionality **6** as potent antimicrobial agents.[12]

Recently, we have discovered 2-(3′-indolyl)-*N*-arylthiazole-4-carboxamides and carbazolyl glyoxamides **7** as anticancer and antibacterial agents.[13,14] Inspired from our previous results and profound antibacterial and anticancer properties of bisindoles, in this report we designed novel bis(indolyl)glyoxylamides by retaining the key structural features of bisindoles and glyoxylamides as depicted in Figure 2.

Bis(indolyl)glyoxylamides **10a–n** were prepared by following the synthetic route illustrated in Scheme 1. *N*-Alkyl indoles **9a–d** were prepared by following the reported reaction condition in 80–92%.[14] Initially, the reaction of indole **9** with oxalyl chloride generated indole-3-glyoxylylchloride. Further reaction of indole-3-glyoxylylchloride with tryptamine afforded bis(indolyl)-glyoxylamide **10** in 82–93% yields.



Scheme 1. Synthesis of bis(indolyl)glyoxylamides **10a–n**.

Preparation of compound **10** was further simplified by performing the reaction in a sequential one-pot fashion. From the reaction of indole **9** and oxalyl chloride in situ generated

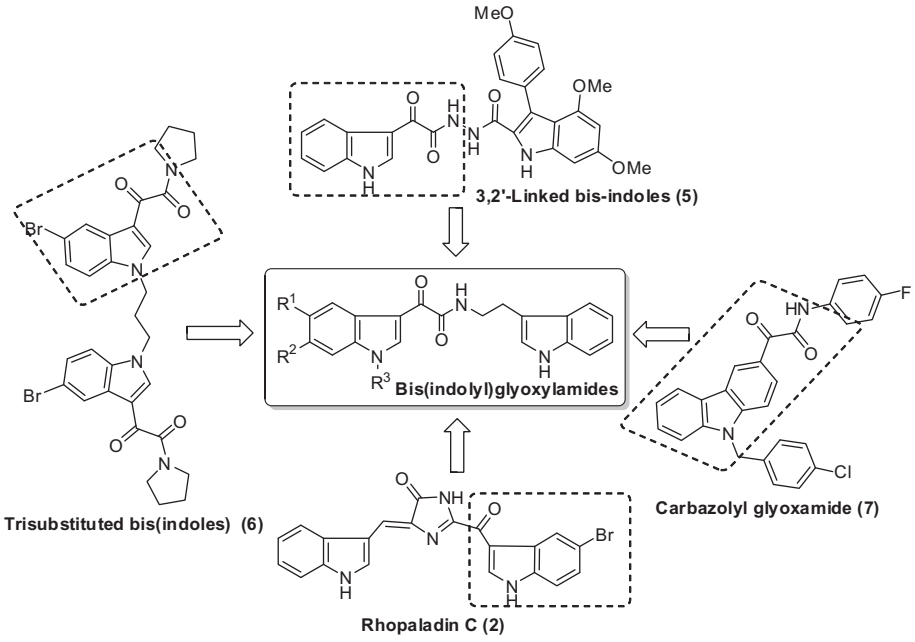
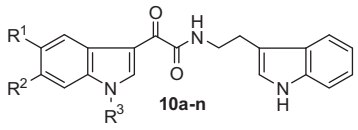


Figure 2. Rational design of bis(indolyl)glyoxylamides **10a–n**.

Table 1
In vitro antibacterial activity of bis(indolyl)glyoxylamides



Compd	R^1	R^2	R^3	ZOI (mm) and MIC (μg/mL) values[a]									
				Gram-negative						Gram-positive			
				E. coli		*P. putida*		*K. pneumoniae*		*B. subtilis*		*S. aureus*	
				ZOI	MIC	ZOI	MIC	ZOI	MIC	ZOI	MIC	ZOI	MIC
10a	H	H	H	15	50	14	50	14	100	15	50	15	50
10b	OMe	H	H	15	100	15	100	15	50	–	–	–	–
10c	Br	H	H	16	50	14	100	15	100	14	100	15	>100
10d	F	H	H	**20**	**12.5**	**18**	**12.5**	**18**	**12.5**	**18**	**>12.5**	17	**25**
10e	H	OMe	H	14	>50	15	>50	15	100	15	>100	14	100
10f	H	F	H	15	100	14	>100	14	>50	–	–	–	–
10g	H	H	CH_3	**18**	**12.5**	17	**>25**	17	**25**	**18**	**>25**	16	**50**
10h	H	H	CH_2CH_3	14	>50	12	>100	13	>100	14	100	14	100
10i	H	H	4-$ClC_6H_4CH_2$	**18**	**12.5**	**18**	**12.5**	**18**	**>12.5**	17	**>25**	17	**>25**
10j	Br	H	4-$ClC_6H_4CH_2$	15	100	14	>100	14	>50	14	100	13	100
10k	MeO	H	4-$ClC_6H_4CH_2$	13	>100	15	50	–	–	–	–	–	–
10l	F	H	4-$ClC_6H_4CH_2$	14	100	14	100	12	>100	13	>50	13	100
10m	H	MeO	4-$ClC_6H_4CH_2$	15	50	16	50	15	>50	–	–	–	–
10n	H	H	4-$FC_6H_4CH_2$	15	100	15	100	13	>100	12	>100	14	>100
Chloramphenicol				**22**	**16**	**21**	**16**	**20**	16	**22**	16	**21**	16

[a] The zone of inhibition and MIC values for compounds with significant activity are shown in bold.

indole-3-glyoxalylchloride was subsequently treated with tryptamine and furnished bis(indolyl)glyoxylamides **10a–n** in 82–93% yields.[15]

Synthesized bis(indolyl)glyoxylamides **10a-n** were initially screened for in vitro antibacterial activity against two Gram-positive bacteria (*Bacillus subtilis* & *Staphylococcus aureus)* and three Gram-negative bacteria (*Escherichia coli*, *Pseudomonas putida*, & *Klebsiella pneumonia*). Chloramphenicol was used as a positive control. The activity results in form of zone of inhibition (ZOI) and minimum inhibitory concentration (MIC)) are given in Table 1.

Unsubstituted bis(indolyl)glyoxylamide **10a** was moderately active against the tested bacterial strains. Introduction of methoxy or bromo group (compounds **10b** and **10c)** at C-5 position of indole ring did not improve the activity. Interestingly, compound **10d** with fluorine substituent exhibited strong antibacterial activity against all the tested bacterial strains with MIC values ranging from 12.5 to 25 μg/mL (ZOI = 17–20 mm). Improved antibacterial activity of **10d** is likely due to the presence of fluorine, which is known to enhance lipophilicity and stability of the molecule.[16] By changing the position (C-5 to C-6) of methoxy and fluoro groups in the indole ring resulted to inactive analogues **10e** and **10f**. Methylation of indole *N*–H led to compound **10g** with four-fold (**10a** vs **10g**) enhanced activity against Gram-negative bacteria *E. coli* (MIC = 12.5 μg/mL). Replacement of *N*-methyl with *N*-ethyl led to dramatic loss in activity (compound **10h**). However, N-alkylation with a bulkier 4-chlorobenzyl group resulted in compound **10i** with significantly improved (four-fold) activity against Gram-negative bacteria *E. coli* and *P. putida* (MIC = 12.5 μg/mL; ZOI = 18 mm). Substituents such as bromo (**10j**), methoxy (**10k** and **10m**) and fluoro (**10l**) in the indole ring or replacement of *N*-4-chlrobenzyl with *N*-4-flourobenzyl (**10n**) resulted in substantial loss of activity (**10i** vs **10j–n**). From the structure–activity relationship study of bis(indolyl)glyoxyl-amides it was established that combination of indole with 5-fluoroindole or *N*-alkyl (methyl or 4-chlorobenzyl) was favorable for the antibacterial activity.

Figure 3 represents the time dependent killing kinetics of antimicrobial active compounds **10d**, **10g** and **10i** against the *E. coli* (Fig. 3A), *P. putida* (Fig. 3B), *B. subtilis* (Fig. 3C) and *S. aureus* (Fig. 3D) bacterial strains. In the case of Gram-negative bacteria, these compounds showed 80–95% bactericidal activity within initial 2 h. This clearly indicates that these compounds showed fastest bactericidal action by quickly inhibiting the bacterial proliferation and thereafter achieving maximum bacterial reduction in the subsequent hour. It is evident from Figure 3 that **10d** was more effective with the higher killing activity when compared to derivatives **10g** and **10i** against Gram-negative bacteria. Similarly, for the Gram-positive bacteria, compounds **10d**, **10g**, and **10i** showed good antibacterial activity by achieving bactericidal effect against *B. subtilis* (>80%) and S. *aureus* (>65%), within initial 2 h of incubation.

After assessing the antibacterial activity of bis(indolyl) glyoxylamides **10a–n**, we next evaluated their cytotoxicity against human embryonic kidney 293 (HEK 293T), human prostate (PC-3 and castration-resistant prostate C4-2), cervical (HeLa), breast (MDA-MB-231) and pancreatic BxPC-3 cancer cell lines using MTT assay. The goal was to not only identify potent antibacterial compounds but also ensure that they display minimal cytotoxicity in mammalian cells. Doxorubicin was used as a reference drug and the activity results are summarized in Table 2. Unsubstituted bis(indolyl)glyoxalylamide **10a** was found to be moderately active with IC_{50} value ranging 38–97 μM against the tested cell lines. Substitution on indole ring was unfavourable for the activity except compound **10f** with 6-fluoro-indole moiety was found to be more cytotoxic towards the tested cancer cells.

Compound **10f** exhibited moderate cytotoxicity against HeLa, PC-3, MDA-MB-231 and BxPC-3 cells with IC_{50} values of 22.34, 24.05, 21.13 and 29.94 μM, respectively. Further, substitution on indole *N*–H resulted in inactive compounds **10g–n**. Most importantly, compounds **10d**, **10g** and **10i**, which displayed potent antibacterial activities, showed no toxicity in any of the human cell lines even at 100 μM concentration, suggesting that these compounds likely target bacterial-specific pathways. Notably, the compound **10d** was found to be stable at pH 4.5 and 7.4 up to 48 h, however, it is sparingly soluble in water (0.3 μg/mL).

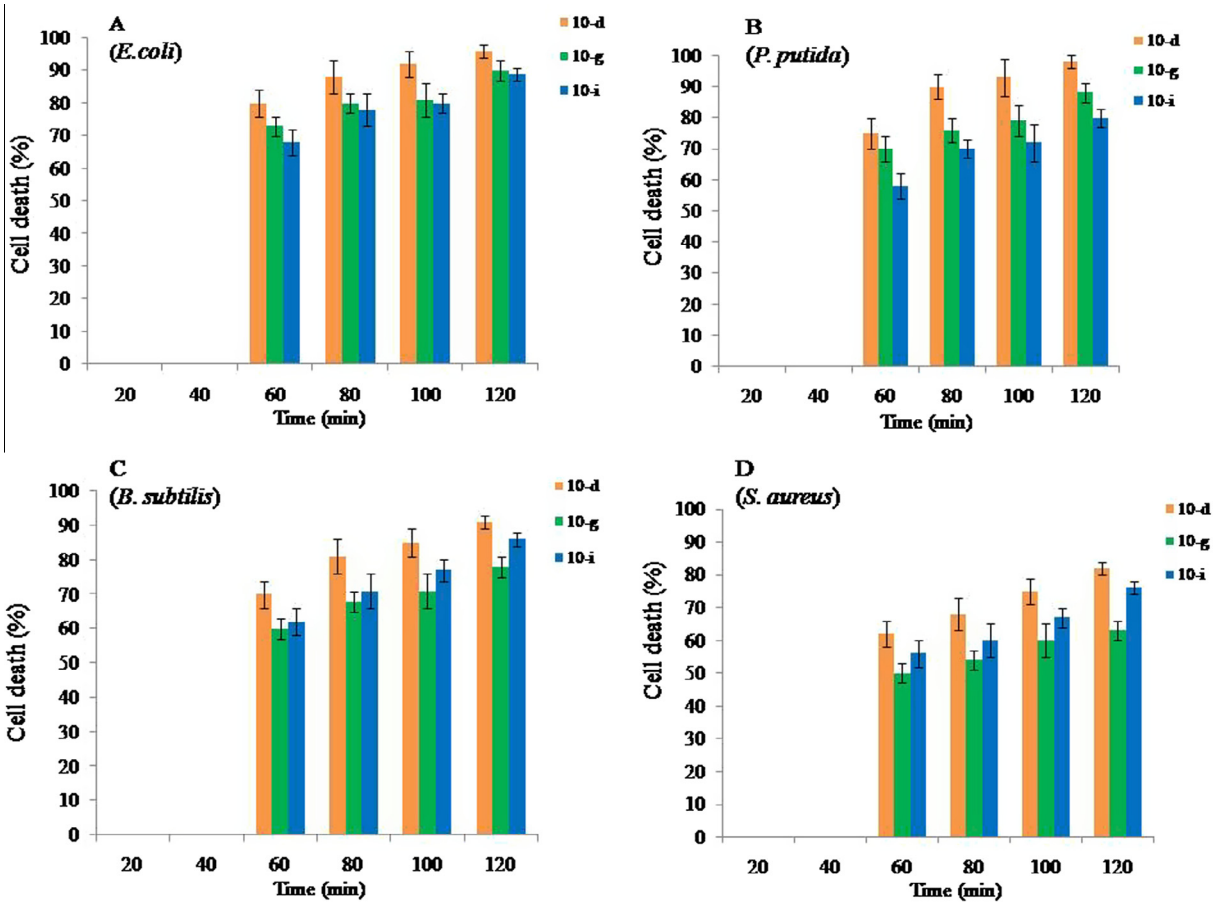
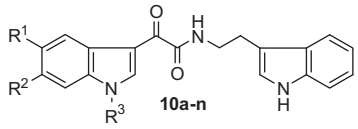


Figure 3. Time dependent killing of *E. coli*, *P. putida*, *B. subtilis* and *S. aureus* upon treatment with **10d**, **10g** and **10i** (3 × MIC).

Table 2
In vitro anticancer activity of bis(indolyl)glyoxylamides



				IC$_{50}$ (μM)[a]					
Compd	R^1	R^2	R^3	HEK 293T	C4-2	HeLa	PC-3	MDA-MB-231	BxPC-3
10a	H	H	H	**97.72**	**71.51**	**48.85**	**38.45**	**48.7**	**63.95**
10b	OMe	H	H	>100	>100	>100	>100	>100	>100
10c	Br	H	H	>100	>100	>100	>100	>100	>100
10d	F	H	H	>100	>100	>100	>100	>100	>100
10e	H	OMe	H	>100	>100	>100	>100	>100	>100
10f	H	F	H	**69.82**	**46.03**	**22.34**	**24.05**	**21.13**	**29.94**
10g	H	H	CH_3	>100	>100	>100	>100	>100	>100
10h	H	H	CH_2CH_3	>100	>100	>100	>100	>100	>100
10i	H	H	4-Cl$C_6H_4CH_2$	>100	>100	>100	>100	>100	>100
10j	Br	H	4-Cl$C_6H_4CH_2$	>100	>100	>100	>100	>100	>100
10k	MeO	H	4-Cl$C_6H_4CH_2$	>100	>100	>100	>100	>100	>100
10l	F	H	4-Cl$C_6H_4CH_2$	>100	>100	>100	>100	>100	>100
10m	H	MeO	4-Cl$C_6H_4CH_2$	>100	>100	>100	>100	>100	>100
10n	H	H	4-F$C_6H_4CH_2$	>100	>100	>100	>100	>100	>100
Doxorubicin				3.1	1.85	5	9.5	6.75	13

[a] IC$_{50}$ values are the mean of three different experiments performed in duplicate.

To determine the mode of cellular death caused by bis(indolyl) glyoxylamides, compounds **10a** (IC$_{50}$ = 38.45 μM,) and **10f** (IC$_{50}$ = 24.05 μM) with moderate cytotoxicity against PC-3 cells, were treated for 48 h, and cleaved PARP1 levels were analyzed using immunoblot analysis. As shown in Figure 4, exposure of PC-3 cells to either **10a** or **10f** resulted in increased levels of

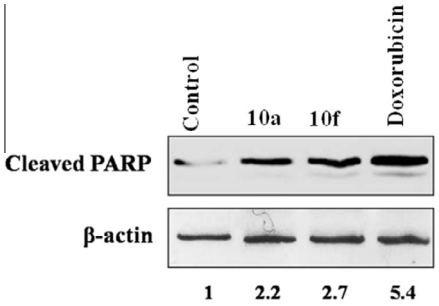


Figure 4. Immunoblot analysis of cleaved PARP1 protein with **10a** and **10f** in PC-3 cells.

cleaved PARP1, thereby, confirming that both the compounds led to apoptotic induced cell death in PC-3 cells.

In summary, we have synthesized and investigated antibacterial and anticancer activities of fourteen novel bis(indolyl)glyoxylamides **10a–n**. Compounds **10d**, **10g** and **10i** were identified with significant activities and could be promising candidates as antibacterial agents. Cell death assay study revealed that **10d** was more effective by exerting higher killing activity against the Gram-negative bacterial pathogens. Furthermore, in anticancer activity evaluation of bis(indolyl)glyoxylamides led to compounds **10a** and **10f** with moderate activity against the tested cancer lines. Exposure of PC-3 cells to either **10a** or **10f** resulted in the enhancement of cleaved PARP1 levels, indicating that bis(indolyl)glyoxylamides induced apoptosis in PC-3 cells.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and characterization data for compounds **10a–n**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2016.04.080.

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15. *General procedure for the preparation of bis(indolyl) glyoxylamides **10a–n**:* To a cooled (0 °C) solution of indole **9** (1.7 mmol) in THF (5 mL) was added oxalyl chloride (0.227 g, 1.7 mmol) and the resulting mixture was stirred at same temperature for 1 h. Subsequently, tryptamine (0.28 g, 1.7 mmol) and triethylamine (1 mL, 5.4 mmol) were added at 25 °C and the contents were allowed to stir for 4 h. Upon completion of the reaction as indicated by TLC, solvent was removed in vacuuo. The residue so obtained was purified by column chromatography using ethyl acetate:hexane as an eluent to obtain pure bis(indolyl)-glyoxalylamides **10a-n** in 82-93% yields.
Spectral data for selected compounds: N-(2-(1H-Indol-3-yl)ethyl)-2-(1H-indol-3-yl)-2-oxoacetamide (***10a***): Yield 87%, off white solid. Mp 199–201 °C (Lit. 198–200 °C);[3b] IR (KBr, ν cm^{-1}) 3402, 3393, 3279, 1666, 1620, 1504, 1435, 1234, 1134; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.27 (s, 1H), 10.86 (s, 1H), 8.85 (t, J = 5.3 Hz, 1H), 8.77 (s, 1H), 8.28–8.19 (m, 1H), 7.61 (d, J = 7.7 Hz, 1H), 7.54 (d, J = 6.0 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.30–7.23 (m, 2H), 7.21 (s, 1H), 7.07 (t, J = 7.4 Hz, 1H), 6.99 (t, J = 7.3 Hz, 1H), 3.54–3.49 (m, 2H), 2.95 (t, J = 7.3 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 182.7, 163.9, 139.0, 136.7, 127.7, 126.7, 123.9, 123.2, 123.0, 121.8, 121.4, 118.8, 118.7, 113.0, 112.6, 112.1, 111.9, 39.9, 25.4; ESI(FAB) m/z calcd for $C_{20}H_{18}N_3O_2$: 332.14 (M+H)$^+$, found 332.15 (M+H)$^+$ and 354.12 (M+Na)$^+$. *5-(1H-Indol-3-yl)-1-(5-methoxy-1H-indol-3-yl)pentane-1,2-dione* (***10b***): Yield 82%, pale yellow solid, m.p. 157-158 °C; IR (KBr, ν cm^{-1}): 3394, 3294, 3202, 1597, 1481, 1435, 1265, 1211, 1142, 802, 741, 447, 401; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.15 (s, 1H), 10.86 (s, 1H), 8.80 (t, J = 5.9 Hz, 1H), 8.71 (d, J = 3.3 Hz, 1H), 7.76 (d, J = 2.4 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.44 (d, J = 8.8 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.21 (d, J = 1.9 Hz, 1H), 7.10–7.06 (m, 1H), 6.99 (t, J = 7.2 Hz, 1H), 6.95–6.85 (m, 1H), 3.80 (s, 3H), 3.54–3.49 (m, 2H), 2.96 (t, J = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 182.4, 164.0, 156.4, 139.0, 136.7, 131.5, 127.7, 123.1, 121.4, 118.8, 118.8, 113.3, 112.5, 112.0, 111.9, 103.9, 55.8, 39.3, 25.3; ESI(FAB) m/z calcd for $C_{21}H_{19}N_3O_3$: 362.39 (M+H)$^+$, found 362.15 (M+H)$^+$ and 384.12 (M+Na)$^+$. *N-(2-(1H-Indol-3-yl)ethyl)-2-(5-bromo-1H-indol-3-yl)-2-oxoacetamide* (***10c***): Yield 84%, yellow solid, mp 198–200 °C; IR (KBr, ν cm^{-1}): 3418, 3256, 1605, 1504, 1435, 1366, 1227, 1219, 1134, 795, 748, 602, 463, 447, 401; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.44 (s, 1H), 10.86 (s, 1H), 8.89 (t, J = 6.0 Hz, 1H), 8.82 (d, J = 3.1 Hz, 1H), 8.36 (d, J = 1.8 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.52 (d, J = 8.6 Hz, 1H), 7.42 (dd, J = 8.6, 2.0 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.20 (d, J = 2.1 Hz, 1H), 7.07 (t, J = 7.0 Hz, 1H), 6.99 (t, J = 7.0 Hz, 1H), 3.54–3.49 (m, 2H), 2.95 (t, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 182.6, 163.5, 140.1, 136.6, 135.5, 128.5, 127.6, 126.5, 123.8, 123.2, 121.4, 118.8, 115.8, 115.2, 112.3, 111.8, 39.3, 25.3; ESI(FAB) m/z calcd for $C_{20}H_{15}BrN_3O_2$: 408.10 (M−H)$^+$, found 408.10 (M-H)$^+$. *N-(2-(1H-Indol-3-yl)ethyl)-2-(5-fluoro-1H-indol-3-yl)-2-oxoacetamide* (***10d***): Yield 93%, cream colour solid, mp 241–242 °C; IR (KBr, ν cm^{-1}): 3410, 3356, 3279, 1659, 1620, 1504, 1435, 1234, 1180, 1134, 802, 741, 447, 401; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.37 (s, 1H), 10.86 (s, 1H), 8.90 (t, J = 6.0 Hz, 1H), 8.84 (s, 1H), 7.92 (dd, J = 9.7, 2.6 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.56 (dd, J = 8.8, 4.6 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.21 (d, J = 2.2 Hz, 1H), 7.17–7.11 (m, 1H), 7.10–7.04 (m, 1H), 7.02–6.96 (m, 1H), 3.55–3.50 (m, 2H), 2.96 (t, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 182.5, 163.6, 160.6, 158.3, 140.4, 136.7, 133.3, 127.7, 127.5, 127.4, 123.2, 121.4, 118.8, 118.7, 114.4, 114.3, 112.7, 112.6, 112.1, 112.0, 111.9, 106.8, 106.6, 39.3, 25.3; ESI(FAB) m/z calcd for $C_{20}H_{17}FN_3O_2$: 350.13 (M+H)$^+$, found 350.12 (M+H)$^+$.
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