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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, anti-inflammatory and anticancer activity evaluation of some mono- and bis-Schiff's bases

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Abstract Several mono-Schiff's bases (**3a–i**) and bis-Schiff's bases (**5a–f**) were synthesized using microwave irradiation technique (**3a–h**, **5a–c**) and by simply grinding at room temperature for a few minutes (**3i**, **5d–f**). All these compounds were characterized by spectroscopic means and elemental analysis. They were screened for anti-inflammatory and anticancer activities (against five human cancer cell lines). Compound **5f** exhibited good anti-inflammatory and compounds **3f**, **5a–f** exhibited good anticancer activity.

Keywords Schiff's bases · Bis-Schiff's bases · Anti-inflammatory · Anticancer evaluation

Introduction

Any kind of health problem is associated with pain, e.g. inflammatory diseases and cancer. To manage pain, various drugs, i.e. phenylbutazone, indomethacin, aspirin, ibuprofen, etc. are available in the market. These drugs cannot be used continuously for a long time as they can cause ulcer (a major side effect) (Wolf, 1981). There are not many drugs available in the market for the effective treatment of cancer. Various research groups are making efforts in search of potent molecules which can be developed as effective and safer anticancer and anti-inflammatory drugs. Schiff's bases are reported to exhibit anti-inflammatory (Jayasekhar *et al.*, 1997; Shalaby and El-Eraky, 1997; Khedekar *et al.*, 2003; Vazzana *et al.*, 2004; Hegazy *et al.*, 2005; Bhandari *et al.*, 2008), antimicrobial (Bawa and Kumar, 2009; Magd–El–Din *et al.*, 2009), antitumor (Kumar and Rajkumar, 2006; Jiang *et al.*, 2008), prostaglandin D_2 production (Tanaka *et al.*, 2005), lipoxygenase (Hadjipavlou-Litina and Geronikaki, 1998; Geronikaki *et al.*, 2003) and MIF tautomerase (Dios *et al.*, 2002) inhibition activities. Schiff's bases are also employed as ligands for the complexation of metal ions (Aydogan *et al.*, 2001). Tempted by wide variety of biological activities exhibited by Schiff's bases and in continuation of our efforts (Sondhi *et al.*, 2010a, b, c, d, 2011) in search of potent molecules exhibiting anti-inflammatory and anticancer activities, a number of mono- and bis-Schiff's bases have been synthesized and screened for anti-inflammatory and anticancer activities which we wish to report in this article.

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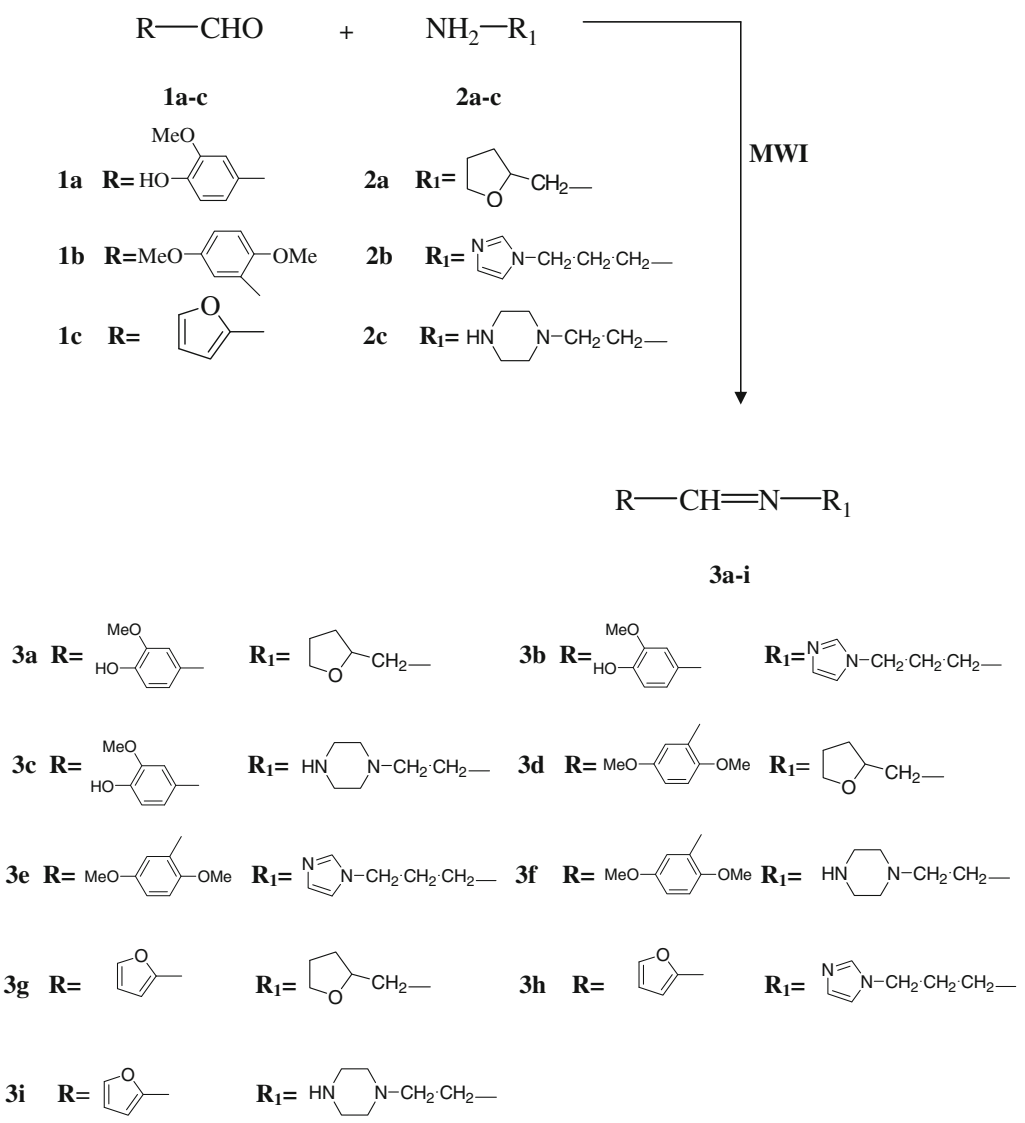
Result and discussion

Microwave oven used has 100, 180, 300, 450, 600, 850 and 1000 W power levels. For optimization of reaction conditions for synthesis of mono- and bis-Schiff's bases, reaction mixtures were irradiated at 100, 180, 300, and 450 W for different intervals of time and progress of reaction was monitored by Thin layer chromatography (TLC). In case of **5b** product formation started at 300 W power level and in case of **3a–h** and **5a** product formation started at 450 W but in case of **5c** product formation took place at 600 W power level. Irradiation time was optimized by monitoring the progress of reaction by TLC. Optimized reaction conditions obtained for various compounds are reported herewith. 4-Hydroxy-3-methoxy benzaldehyde (**1a**; Scheme 1) and

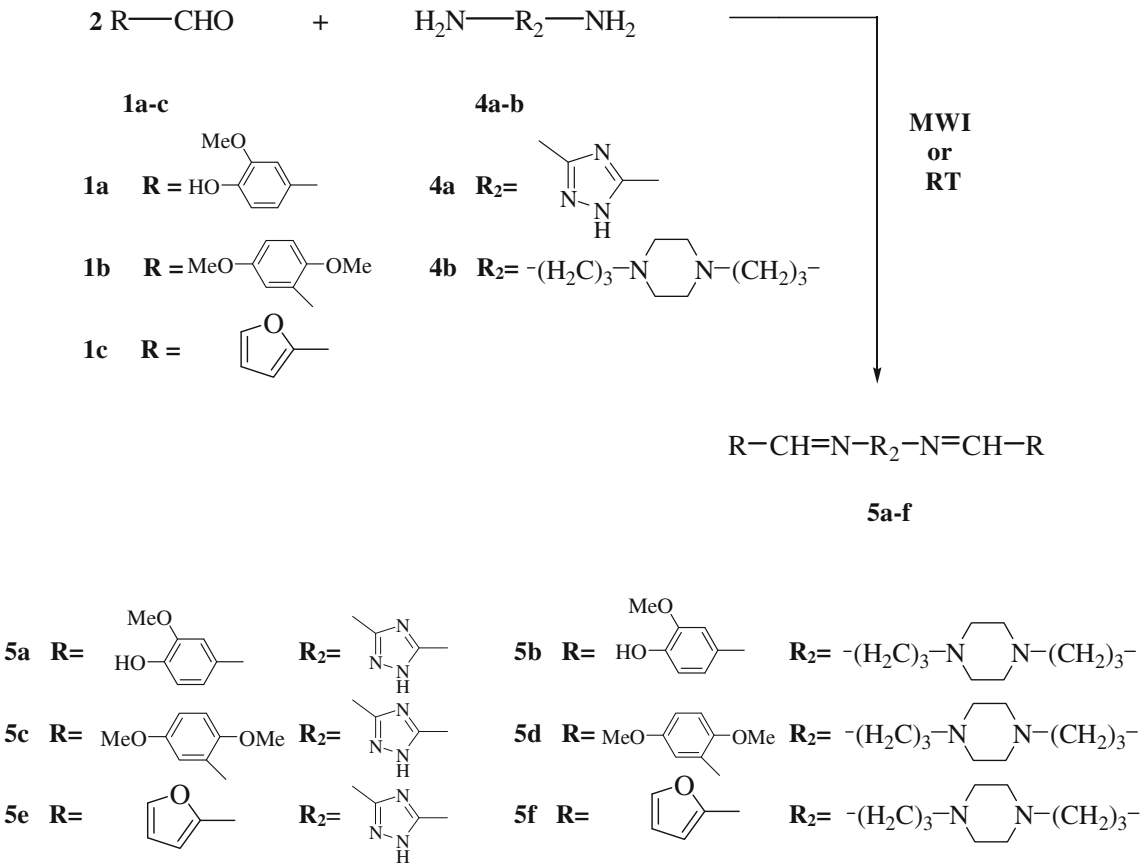


Scheme 1 Synthesis of Schiff's bases

tetrahydrofurfuryl amine (**2a**; Scheme 1) were taken in equimolar ratio and mixed together thoroughly in a petri dish. This reaction mixture was subjected to microwave irradiation at 450 W power level for 4 min. Progress of the reaction was monitored by TLC. The reaction mixture was further irradiated at 450 W for 4 min two times. The total irradiation time is 12 min. TLC of reaction mixture showed completion of reaction. This reaction mixture was dissolved in $CHCl_3$ and washed with water. Chloroform layer was dried over anhydrous sodium sulphate. Solvent was removed under reduced pressure to give pure condensed product **3a** in 85% yield. ^{1}H NMR (500 MHz; DMSO-d_6) of **3a** shows signals at δ (ppm): 1.590–1.632 (m, 1H, one H of CH_2), 1.775–1.839 (m, 2H, CH_2), 1.920–1.947 (m, 1H, one H of CH_2), 3.506–3.544 (m, 1H, one H of CH_2), 3.570–3.631 (m, 2H, CH_2), 3.711–3.754 (m, 1H, one H of CH_2), 3.798 (s, 3H, $-OCH_3$), 4.044–4.067 (m, 1H, >CH–), 6.814–6.831 (d, 1H, Ar), 7.103–7.123 (dd, 1H, Ar), 7.323–7.327 (d, 1H, Ar), 8.154 (s, 1H, –CH=) GC–MS *m/z* 235 (M^+, 3.39%). FT-IR spectra show absorption band at 3422 (–OH), 1650 (–C=N–), 1543 and 1508 (Ar) cm^{-1}. Spectral data of **3a** fully support the structure assigned to it. Similarly, condensation of 4-hydroxy-3-methoxy benzaldehyde (**1a**) with 1-(3-aminopropyl) imidazole (**2b**) and 1-(2-aminoethyl) piperazine (**2c**); 2,5-dimethoxy benzaldehyde (**1b**) with **2a**–**c**; 2-furaldehyde (**1c**) with **2a**, **b** gave condensation products **3b**, **c**; **3d**–**f** and **3g**, **h**, respectively. Power level, irradiation time, yield, spectral and analytical data of compounds **3b**–**h** are reported in "experimental" section of this article. Spectral and analytical data of **3b**–**h** fully support the structures assigned to them. 2-Furaldehyde (**1c**) and 1-(2-aminoethyl) piperazine (**2c**) were mixed together in equimolar

ratio. The reaction mixture was hand ground for 15 min in a pestle mortar. The reaction mixture gets heated up during grinding. It was further allowed to stand at room temperature for half an hour. This thick mass was dissolved in $CHCl_3$ and washed with water. $CHCl_3$ layer was dried over sodium sulphate (anhydrous). Removal of solvent under reduced pressure gave condensed product furan-2-ylmethylene-2(piperazin-1-yl ethyl) amine (**3i**) in 86% yield. ^{1}H NMR (500 MHz; DMSO-d_6) of **3i** shows signals at δ (ppm): 2.339–2.519 (m, 10H, 5 × CH_2), 3.605–3.632 (m, 2H, =N–CH_2–), 6.604–6.615 (q, 1H, Ar), 6.890–6.897 (d, 1H, Ar), 7.806–7.809 (d, 1H, Ar), 8.155 (s, 1H, –CH=) GC–MS *m/z* 207 (M^+, 31.89%). FT-IR spectra show absorption band at 3440 (NH), 1650 (–C=N–), 1458 (Ar) cm^{-1}. Spectral data of **3i** is in full agreement with the structure assigned to it. 4-Hydroxy-3-methoxy benzaldehyde (**1a**) and 3, 5-diamino-1,2,4-triazole (**4a**; Scheme 2) were taken together in 2:1 molar ratio, respectively, and mixed together thoroughly. This reaction mixture was subjected to microwave irradiation at 450 W power level for 5 × 4 min. TLC of reaction mixture indicate completion of reaction. This solid product was recrystallized from methanol to give pure product **5a** (Scheme 2) in 88% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 3.876 (s, 6H, OCH_3 + OCH_3), 6.917–6.966 (q, 2H, Ar), 7.399–7.415 (d, 1H, Ar), 7.488–7.503 (d, 1H, Ar), 7.599 (s, 2H, Ar), 9.088–9.136 (2s looks like a doublet, 2H, –CH= + –CH=), 9.902 (s, 1H, exch, OH,), 10.155 (s, 1H, exch, OH,), 13.901 (s, 1H, exch, NH) GC–MS *m/z* 367 (M^+, 2.15%). FT-IR spectra show absorption band at 3341 (NH), 1671 (–C=N–), 1588 and 1573 (Ar) cm^{-1}. Spectral data of **5a** fully support the structure assigned to it. Similarly, condensation of 4-hydroxy-3-methoxy benzaldehyde (**1a**) with 1,4-bis (3-aminopropyl) piperazine (**4b**; Scheme 2) and 2,5-dimethoxy benzaldehyde (**1b**) with 3,5-diamino-1,2,4 triazole (**4a**; Scheme 2) gave bis-Schiff's bases **5b** and **c** in 79 and 80% yield, respectively. Spectral and analytical data of **5b** and **c** reported in "experimental" section of this article fully support the structures assigned to them.

2,5-Dimethoxy benzaldehyde (**1b**) and 1,4-bis (3-aminopropyl) piperazine (**4b**) were mixed together in 2:1 molar ratio, respectively. This reaction mixture was hand ground in a small pestle mortar for half an hour. The crude product so obtained was crystallized from chloroform to give pure bis-Schiff's base **5d** (Scheme 2) in 83% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.875–1.932 (m, 4H, 2 × CH_2), 2.346–2.518 (m, 12H, 6 × CH_2), 3.643–3.669 (t, 4H, 2 × CH_2), 3.817 (s, 6H, 2 × OCH_3), 3.834 (s, 6H, 2 × OCH_3), 6.852–6.870 (d, 2H, Ar), 6.940–6.964 (dd,



Scheme 2 Synthesis of bis-Schiff's bases

2H, Ar), 7.429–7.486 (d, 2H, Ar), 8.643 (s, 2H, 2 × –CH=) GC–MS *m/z* 496 (M^+, 0.50%). FT-IR spectra show absorption band at 1628 (–C=N–), 1499 and 1464 (Ar) cm^{-1}. Spectral data of **5d** fully support the structure assigned to it.

Similarly, condensation of 2-furaldehyde (**1c**) with 3,5-diamino-1,2,4 triazole and 1,4-bis(3-aminopropyl) piperazine gave bis-Schiff's bases **5e** and **f**, respectively, in 77 and 87% yield. Spectral and analytical data of **5e** and **f** reported in experimental section of this article fully support the structures assigned to them.

All the compounds were also prepared by using microwave reactor model CEM DISCOVER MODEL NO 908010. Reaction temperature for **5b**, **3a–h**, **5a** and **c** was 75, 80 and 100°C respectively. Irradiation time for each compound was same as mentioned in experimental section of this article.

Over-expression of prostaglandin cascade and COX-2 are involved in carcinogenesis (Brown and DuBios, 2005; Grosch *et al.*, 2006; Harris 2009), non-steroidal anti-inflammatory drugs (non-selective or selective cox-2 inhibitors) exhibit strong potential for chemoprevention of cancer (Xiao *et al.*, 2006; Harris *et al.*, 2007, 2008). In view of above information from literature it is considered worthwhile to screen newly synthesized compounds for anti-inflammatory and anticancer activities. Compounds **3a–i** and **5a–f** were screened for anti-inflammatory activity at a dose of 50 mg/kg p.o. using carrageenan-induced paw oedema model (Winter *et al.*, 1962) and results are summarized in Table 1. In vitro anticancer activity (Skehan et al., 1990; Monks *et al.* 1991) evaluation of compounds **3a–i** and **5a-f** was carried out against five human cancer cell lines consisting of lung (NCI H-522), ovary (PA1), breast (T47D), colon (HCT-15) and liver (HepG2). Percentage (%) growth inhibition of cancer cell lines was determined at a concentration of 1×10^{-5}M and results are summarized in Table 1.

It is observed that compounds **3h** and **5f** exhibited good anti-inflammatory activity. This may be due the fact that furan ring is attached through a flexible three carbon chain which may be making these compounds favourable electronically and stereochemically for interaction with the active site and thus showing good anti-inflammatory activity.

Results in Table 1 indicate that compounds **3f** (lung NCI H-522), **5a–f** (ovary PA1) and **5c** (breast T47D) exhibited good anticancer activity against the cell lines mentioned in the brackets. These activities may be due to the fact that these molecules meet stereochemical and electronic requirements of the target in a better way as compared to other molecules.

Conclusion

Synthesis of mono- and bis-Schiff's bases **3a–h** and **5a–c** by microwave irradiation and **3i** and **5d–f** by hand ground

Table 1 Anti-inflammatory and in vitro anticancer activity of compounds **3a–i** and **5a–f**

Compound no.	Anti-inflammatory activity (%) at 50 mg/kg p.o.	Lung NCI H-522	Ovary PA1	Breast T47D	Colon HCT-15	Liver HepG2
3[a]	14	17	13	25	24	01
3b	00	22	16	15	01	11
3c	18	25	39	25	04	30
3d	16	15	38	33	00	25
3e	00	24	25	29	03	24
3f	21	**49**	16	28	04	22
3 g	26	15	16	12	04	20
3 h	**28**	29	13	16	01	01
3i	22	19	35	21	05	18
5a	26	09	**40**	38	04	14
5b	25	01	**51**	18	05	03
5c	22	15	**53**	**41**	05	10
5d	20	13	**62**	24	07	08
5e	11	26	**48**	30	03	25
5f	**30**	05	**43**	09	06	10
Ibuprofen	39	–	–	–	–	–
Cyclophosphamide	–	07	21	36	07	24
Cycloheximide	–	20	82	30	05	14
Actinomycin-D	–	59	93	21	49	42
5-Fluorouracil	–	51	27	22	21	33

Bold values represent compounds showing good anti-inflammatory and anticancer activity

at room temperature is reported in this article. Anti-inflammatory and anticancer activity evaluations of **3a–i** and **5a–f** were carried. Compounds **3h** and **5f** showed good anti-inflammatory activity and compounds **3f** (lung NCI H-522), **5a–f** (ovary PA1) and **5c** (breast T47D) showed good anticancer activity.

Experimental

Chemistry

Melting points (mp) were determined on a JSGW apparatus and are uncorrected. Microwave oven model M 197DL (SAMSUNG) and microwave reactor model CEM DISCOVER MODEL NO 908010 were used for microwave irradiation. IR spectra were recorded using a perkin Elmer 1600FT spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker WH 500 spectrometer at a ca 5–15% (W/V) solution in DMSO-d_6 and $CDCl_3$ (TMS as internal standard). GC–MS was recorded on Perkin Elmer Calrus 500 mass spectrometer. Elemental analysis was carried out on a vario ELIII elementar. TLC was performed on silica gel G for TLC (Merck) and spots were visualized by iodine vapour. Starting materials i.e. **1a–c**, **2a–c** and **4a–b** were purchased from Aldrich Chemical Company and were used as such.

*General procedure for synthesis of Schiff's bases (**3a–h**)*

*2-Methoxy-4[(tetrahydrofuran-2-ylmethylimino)-methyl] phenol (**3a**)* 4-Hydroxy-3-methoxy benzaldehyde (304 mg; 2 mmol) and tetrahydrofurfuryl amine (0.20 ml; 2 mmol) were mixed thoroughly and irradiated at 450 W for 4 × 3 min. This reaction mixture was taken in $CHCl_3$ and washed with water. $CHCl_3$ layer was dried over anhydrous sodium sulphate. Removal of $CHCl_3$ under reduced pressure gave pure compound **3a**.

Power level 450 W, Irradiation time 4 × 3 min, solvent for TLC $CHCl_3$/MeOH (9.5:0.5), Yield (85%), liquid, IR (KBr) ν_{max}: 3422 (–OH), 1650 (–C=N–), 1543 and 1508 (Ar) cm^{-1}. ^{1}H NMR (500 MHz; DMSO-d_6) δ (ppm): 1.590–1.632 (m, 1H, one H of –CH_2–), 1.775–1.839 (m, 2H, –CH_2–), 1.920–1.947 (m, 1H, one H of –CH_2–), 3.506–3.544 (m, 1H, one H of –CH_2–), 3.570–3.631 (m, 2H, –CH_2–), 3.711–3.754 (m, 1H, one H of –CH_2–), 3.798 (s, 3H, –OCH_3), 4.044–4.067 (m, 1H, >CH–), 6.814–6.831 (d, 1H, J = 8.5 Hz, Ar), 7.103–7.123 (dd, 1H, J = 1.5, 8.5 Hz, Ar), 7.323–7.327 (d, 1H, J = 2 Hz, Ar), 8.154 (s, 1H, –CH=). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 25.1 (C), 28.7 (C), 32.0 (C), 42.6 (C), 55.5 (C), 60.3 (C), 64.9 (C), 67.1 (C), 77.2 (C), 77.9 (C), 109.8 (C), 115.1 (C), 147.9 (C) and 161.2 (C) GC–MS m/z 235 (M^+, 3.39%). Anal. calcd. for $C_{13}H_{17}NO_3$ C 66.38; H 7.23; N 5.95 Found C 66.30; H 7.30; N 6.05.

By following above procedure compounds **3b–h** were synthesized.

*4-[(3-Imidazol-1-yl-propylimino)-methyl]-2-methoxy phenol (**3b**)* Power level 450 W, Irradiation time 2 min, solvent for TLC $CHCl_3$/MeOH (9.5:0.5), Yield 88%, liquid, IR (KBr) ν_{max}: 3394 (–OH), 1640 (–C=N–), 1593 and 1513 (Ar) cm^{-1}. ^{1}H NMR (500 MHz; DMSO-d_6) δ (ppm): 2.038–2.093 (m, 2H, CH_2), 3.467–3.496 (m, 2H, CH_2), 3.824 (s, 3H, –OCH_3), 4.047–4.075 (t, 2H, J = 7 Hz, CH_2), 6.828–6.844 (d, 1H, J = 8 Hz, Ar), 6.901 (s, 1H, Ar), 7.130–7.149 (dd, 1H, J = 1.5 Hz, 8 Hz, Ar), 7.172–7.177 (t, 1H, J = 1.5 Hz, Ar), 7.345–7.349 (d, 1H, J = 2 Hz, Ar), 7.614 (s, 1H, Ar), 8.181 (s, 1H, –CH=). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 31.9 (C), 44.2 (C), 48.6 (C), 55.4 (C), 57.1 (C), 109.9 (C), 115.2 (C), 119.3 (C), 122.8 (C), 128.2 (C), 137.2 (C), 147.9 (C), 149.6 (C) and 161.0 (C) GC–MS m/z 259(M^+, 1.55%). Anal. calcd for $C_{14}H_{17}N_3O_2$ C 64.86; H 6.56; N 16.21 Found C 64.80; H 6.60; N 16.25.

*2-Methoxy-4-[(2-piperazin-1-yl-ethylimino)-methyl]-phenol (**3c**)* Power level 450 W, Irradiation time 5 × 2 min, solvent for TLC $CHCl_3$/MeOH (9.5:0.5), Yield 83%, mp 50°C, IR (KBr) ν_{max}: 3410 (NH, OH), 1644 (–C=N–), 1584 and 1505 (Ar) cm^{-1}. ^{1}H NMR (500 MHz; $CDCl_3$) δ (ppm): 2.541 (bs, 4H, 2 × CH_2), 2.673–2.702 (t, 2H, J = 7.0 Hz, CH_2), 2.908–2.927 (t, 4H, J = 5 Hz, 2 × CH_2), 3.735–3.764 (t, 2H, J = 7 Hz, CH_2), 3.933 (s, 3H, –OCH_3), 6.921–6.937 (d, 1H, J = 8 Hz, Ar), 7.077–7.093 (d, 1H, J = 8 Hz, Ar), 7.400 (s, 1H, Ar), 8.190 (s, 1H, –CH=) ^{13}C NMR (125 MHz, DMSO-d_6) δ: 25.1 (C), 45.1 (C), 53.6 (C), 55.3 (C), 57.8 (C), 59.3 (C), 66.9 (C), 109.7 (C), 115.2 (C), 122.7 (C), 128.4 (C), 147.9 (C), 149.7 (C) and 161.0 (C) GC–MS m/z 263 (M^+, 6.60%). Anal. calcd. For $C_{14}H_{21}N_3O_2$ C 63.87; H 7.98; N 15.96 Found C 63.82; H 8.05; N 16.05.

*2,5-Dimethoxy-benzylidene-(tetrahydrofuran-2yl methyl)-amine (**3d**)* Power level 450 W, Irradiation time 4 × 3 min, solvent for TLC $CHCl_3$/MeOH (9.5:0.5), Yield 81%, liquid, IR (KBr) ν_{max}: 1638 (–C=N–), 1496 and 1464 (Ar) cm^{-1}. ^{1}H NMR (500 MHz; DMSO-d_6) δ (ppm): 1.590–1.659 (m, 1H, one H of CH_2), 1.752–1.878 (m, 2H, CH_2), 1.928–1.968 (m, 1H, one H of CH_2), 3.565–3.605 (m, 2H, CH_2), 3.641–3.677 (m, 1H, one H of CH_2), 3.727–3.759 (s + m, 4H, –OCH_3 + one H of CH_2), 3.803 (s, 3H, –OCH_3), 4.053–4.103 (m, 1H, >CH–), 7.027–7.039 (m, 2H, Ar), 7.350–7.356 (d, 1H, J = 3 Hz, Ar), 8.584 (s, 1H, –CH=) ^{13}C NMR (125 MHz, DMSO-d_6) δ: 25.2 (C), 28.8 (C), 55.3 (C), 56.0 (C), 65.4 (C), 67.2 (C), 77.8 (C), 110.2 (C), 113.2 (C), 117.9 (C), 124.4 (C), 152.8 (C), 153.0 (C) and 156.7 (C), GC–MS m/z 249 (M^+, 13.65%) Anal. calcd. For $C_{14}H_{19}NO_3$ C 67.46; H 7.63; N 5.62 Found C 67.50; H 7.72; N 5.60.

2,5-Dimethoxy-benzylidene-(3-imidazol-1-yl-propyl)-amine ***(3e)*** Power level 450 W, Irradiation time 4 × 3 min, solvent for TLC $CHCl_3$/MeOH (9.5:0.5), Yield 85%, liquid, IR (KBr) ν_{max}: 1636 (–C=N–), 1496 (Ar) cm^{-1}. ^1H NMR (500 MHz; DMSO-d_6) δ (ppm): 2.046–2.074 (m, 2H, CH_2), 3.503–3.529 (t, 2H, $J = 7$ Hz, CH_2), 3.740 (s, 3H, $–OCH_3$), 3.806 (s, 3H, $–OCH_3$), 4.034–4.062 (t, 2H, $J = 7$ Hz, CH_2), 6.899 (s, 2H, Ar), 7.037–7.047 (t, 1H, $J = 2.5$ Hz, Ar), 7.207 (s, 1H, Ar), 7.364–7.369 (d, 1H, $J = 2.5$ Hz, Ar), 7.633 (s, 1H, Ar), 8.598 (s, 1H, –CH=) ^{13}C NMR (125 MHz, DMSO-d_6) δ: 31.7 (C), 43.5 (C), 55.2 (C), 56.1 (C), 57.6 (C), 110.1 (C), 113.1 (C), 117.9 (C), 119.2 (C), 124.2 (C), 128.2 (C), 137.1 (C), 152.7 (C), 152.9 (C) and 156.34 (C) GC–MS *m/z* 273 (M^+, 18.53%) Anal. calcd. For $C_{15}H_{19}N_3O_2$ C 65.93; H 6.95; N 15.38 Found C 66.02; H 7.00; N 15.42.

2,5-Dimethoxy-benzylidene-(2-piperazin-1-yl-ethyl)-amine ***(3f)*** Power level 450 W, Irradiation time 4 × 4 min, solvent for TLC $CHCl_3$/MeOH (9.0:1.0), Yield 80%, liquid, IR (KBr) ν_{max}: 3415 (–NH–), 1637 (–C=N–), 1495 and 1463 (Ar) cm^{-1}. ^1H NMR (500 MHz; $CDCl_3$) δ (ppm): 2.516 (bs, 4H, 2 × CH_2), 2.660–2.689 (t, 2H, $J = 7$ Hz, CH_2), 2.878–2.897 (t, 4H, $J = 5$ Hz, 2 × CH_2), 3.751–3.782 (m, 2H, CH_2), 3.789 (s, 3H, $–OCH_3$), 3.812 (s, 3H, $–OCH_3$), 6.830–6.848 (d, 1H, $J = 9$ Hz, Ar), 6.919–6.943 (dd, 1H, $J = 3$ Hz, 9 Hz, Ar), 7.449–7.455 (d, 1H, $J = 3$ Hz, Ar), 8.680 (s, 1H, –CH=) ^{13}C NMR (125 MHz, DMSO-d_6) δ: 45.5 (C), 48.5 (C), 54.3 (C), 55.3 (C), 56.0 (C), 58.4 (C), 59.3 (C), 99.5 (C), 110.2 (C), 113.3 (C), 117.9 (C), 124.5 (C), 152.8 (C), 153.0 (C) and 156.4 (C) GC–MS *m/z* 277 (M^+, 3.72%) Anal. calcd. For $C_{15}H_{23}N_3O_2$ C 64.98; H 8.30; N 15.16 Found C 65.08; H 8.36; N 15.20.

Furan-2-yl methylen-(tetrahydro-furan-2-yl)-amine ***(3g)*** Power level 450 W, Irradiation time 3 × 2 min, solvent for TLC $CHCl_3$/MeOH (9.5:0.5), Yield 87%, liquid, IR (KBr) ν_{max}: 1635 (–C=N–), 1511 and 1466 (Ar) cm^{-1}. ^1H NMR (500 MHz; DMSO-d_6) δ (ppm): 1.591–1.632 (m, 1H, one H of CH_2), 1.797–1.839 (m, 2H, CH_2), 1.937 (m, 1H, one H of CH_2), 3.523–3.549 (m, 1H, one H of CH_2), 3.591–3.635 (m, 2H, CH_2), 3.709–3.752 (m, 1H, one H of CH_2), 4.032–4.055 (m, 1H, –CH=), 6.611–6.622 (q, 1H, $J = 2$ Hz, 3.5 Hz, Ar), 6.910–6.916 (d, 1H, $J = 3$ Hz, Ar), 7.816–7.819 (d, 1H, $J = 1.5$ Hz, Ar), 8.140 (s, 1H, –CH=) ^{13}C NMR (125 MHz, DMSO-d_6) δ: 25.1 (C), 28.4 (C), 41.1 (C), 42.5 (C), 67.1 (C), 67.2 (C), 76.9 (C), 77.2 (C), 99.5 (C) and 161.2 (C) GC–MS *m/z* 179 (M^+, 32.22%) Anal. calcd. For $C_{10}H_{13}NO_2$ C 67.03; H 7.26; N 7.82 Found C 67.08; H 7.30; N 7.80.

Furan-2-yl methylene-(3-imidazol-1-yl-propyl)-amine ***(3h)*** Power level 450 W, Irradiation time 3 × 3 min, solvent for TLC $CHCl_3$/MeOH (9.2:0.8), Yield 79%, liquid, IR (KBr) ν_{max}: 1658 and 1636 (–C=N–), 1513 (Ar) cm^{-1}. ^1H NMR (500 MHz; DMSO-d_6) δ (ppm): 2.014–2.070 (m, 2H, CH_2), 3.451–3.479 (m, 2H, CH_2), 4.013–4.042 (m, 2H, CH_2), 6.618–6.628 (q, 1H, $J = 1.5$ Hz, 3.0 Hz, Ar), 6.896–6.900 (t, 1H, $J = 1$ Hz, Ar), 6.922–6.928 (d, 1H, $J = 3$ Hz, Ar), 7.199–7.203 (t, 1H, $J = 2$ Hz, Ar), 7.634 (s, 1H, Ar), 7.826–7.829 (d, 1H, $J = 1.5$ Hz, Ar), 8.155 (s, 1H, –CH=) ^{13}C NMR (125 MHz, DMSO-d_6) δ: 31.8 (C), 43.9 (C), 57.4 (C), 111.9 (C), 114.3 (C), 119.3(C), 128.4(C), 137.2(C), 145.2(C), 150.5(C) and 151.3(C) GC–MS *m/z* 203 (M^+, 74.83%) Anal. calcd. For $C_{11}H_{13}N_3O$ C 65.02; H 6.40; N 20.68 Found C 65.08; H 6.46; N 20.70.

Synthesis of furan-2-yl methylene-(2-piperazin-1-yl-ethyl) amine ***(3i)*** Furan-2-carboxaldehyde (0.20 ml; 2 mmol) and 1-(2-aminoethyl) piperazine (0.26 ml; 2 mmol) were taken together and grinded for about 10 min. The reaction contents get heated during mixing and grinding. This reaction mixture was allowed to stand at room temperature for about half an hour. Reaction contents were taken in $CHCl_3$ (15 ml) and washed with water (2 × 5 ml). Chloroform layer was dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure to give pure product **3i**.

Grinding by hand at room temperature, solvent for TLC $CHCl_3$/MeOH (9.2:0.8), Yield (86%), liquid, IR (KBr) ν_{max}: 3440 (–NH–), 1650 (–C=N–), 1458 (Ar) cm^{-1}. ^1H NMR (500 MHz; DMSO-d_6) δ (ppm): 2.339–2.519 (m, 10H, 5 × CH_2), 3.605–3.632 (m, 2H,=N–CH_2–), 6.604–6.615 (q, 1H, $J = 2$ Hz, 3.5 Hz, Ar), 6.890–6.897 (d, 1H, $J = 3.5$ Hz, Ar), 7.806–7.809 (d, 1H, $J = 1.5$ Hz, Ar), 8.155 (s, 1H, –CH=) ^{13}C NMR (125 MHz, DMSO-d_6) δ: 15.1 (C), 48.6 (C), 53.2 (C), 58.4 (C), 64.9 (C), 99.5 (C), 111.9 (C), 113.9 (C), 145.1 (C), 150.4 (C) and 151.4 (C) GC–MS *m/z* 207 (M^+, 31.89%) Anal. calcd. For $C_{11}H_{17}N_3O$ C 63.76; H 8.21; N 20.28 Found C 63.85; H 8.42; N 20.01.

Synthesis of N^3, N^5-bis (4-hydroxy, 3-methoxy benzylidene)-1H-1,2,4-triazole-3,5-diamine ***(5a)*** 4-Hydroxy-3-methoxy benzaldehyde (304 mg; 2 mmol) and 3,5-diamino-1,2,4-triazole (99 mg; 1 mmol) were mixed together thoroughly. This reaction was irradiated for 5 × 4 min at a power level of 450 W. Condensation product so obtained was washed with diethyl ether and then crystallized from methanol to give pure product **5a**.

Power level 450 W, Irradiation time 5 × 4 min, solvent for TLC $CHCl_3$/MeOH (9.2:0.8), Yield (88%), mp 208°C, IR (KBr) ν_{max}: 3341 (NH), 1671 (–C=N–), 1588 and 1573 (Ar) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ (ppm): 3.876 (s, 6H, OCH_3 + OCH_3), 6.917–6.966 (q, 2H, Ar), 7.399–7.415 (d, 1H, $J = 8$ Hz, Ar),7.488–7.503 (d, 1H, $J = 7.5$ Hz,

Ar), 7.599 (s, 2H, Ar), 9.088–9.136 (2s looks like a doublet, 2H, –CH= + –CH=), 9.902 (s, 1H, –OH, exch), 10.155 (s, 1H, –OH, exch), 13.901 (s, 1H, -NH-, exch) ^{13}C NMR (125 MHz, DMSO-d_6) δ : 55.5 (C), 109.9 (C), 110.5 (C), 110.7 (C), 115.4 (C), 115.5 (C), 126.1 (C), 128.8 (C), 148.0 (C), 148.1 (C), 150.5 (C), 152.9 (C) and 191.0 (C) GC–MS *m/z* 367 (M^+, 2.15%) Anal. calcd. For $C_{18}H_{17}N_5O_4$ C 58.85; H 4.63; N 19.07 Found C 58.60; H 4.60; N 19.28.

*4-(3-(4-(3-(4-hydroxy-3-methoxy benzylideneamine) propyl) piperazin-1-yl)-propylimino)-methyl)-2-methoxy phenol (**5b**)* Power level 300 W, Irradiation time 3 × 3 min, solvent for TLC $CHCl_3$/MeOH (9.5:0.5), Yield 79%, mp 196–198°C, IR (KBr) ν_{max}: 3500 (–OH), 1648 (–C=N–), 1586 and 1517 (Ar) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.880–1.938 (m, 4H, 2 × CH_2), 2.434–2.525 (t + bs, 12H, 6 × CH_2), 3.617–3.644 (t, 4H, J = 7 Hz, 2 × CH_2), 3.970 (s, 6H, 2 × -OCH_3), 6.939–6.956 (d, 2H, J = 8.5 Hz, Ar), 7.089–7.108 (dd, 2H, J = 1.5 Hz, 8 Hz, Ar), 7.431 (s, 2H, Ar), 8.188 (s, 2H, 2 × –CH=) ^{13}C NMR (125 MHz, DMSO-d_6) δ: 27.8 (C), 52.8 (C), 55.4 (C), 55.5 (C), 55.7 (C), 58.3 (C), 109.7 (C), 110.4 (C), 115.2 (C), 115.4 (C), 122.6 (C), 127.6 (C), 128.2 (C), 147.9 (C), 148.3 (C), 153.8 (C), 160.3 (C) and 190.9(C), GC–MS *m/z* 468 (M^+, 2.96%) Anal. calcd. For $C_{26}H_{36}N_4O_4$ C 66.66; H 7.69; N 11.96 Found C 61.02; H 7.75; N 12.08.

*N^3,N^5-bis(2,5-dimethoxy benzyl diene)-1H-1,2,4-triazole-3,5-diamine (**5c**)* Power level 600 W, Irradiation time 5 × 4 min, solvent for TLC $CHCl_3$/MeOH (9.2:0.8), Yield 80%, mp 122°C, IR (KBr) ν_{max}: 1607 (–C=N–), 1498 and 1426 (Ar) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 3.803–3.919 (d, 12H, 4 × OCH_3), 7.173 (s, 4H, Ar), 7.579 (s, 2H, Ar), 9.540 (s, 2H, 2 × –CH=), 14.182 (s, 1H, N, exch) ^{13}C NMR (125 MHz, DMSO-d_6) δ: 55.4 (C), 55.5 (C), 56.2(C), 109.4 (C), 109.5 (C), 113.6 (C), 119.8 (C), 124.1 (C), 153.2 (C), 154.0 (C), 156.2 (C), 156.4 (C) and 163.9 (C) Anal. calcd. For $C_{20}H_{21}N_4O_5$ C 60.75; H 5.31; N 17.72 Found C 61.08; H 5.35; N 17.80.

*3,5-Dimethoxybenzylidene-[3-(4-(3-(2,5-dimethoxy-benzylidene amino)-propyl) piperazin-1-yl)-propyl) amine (**5d**)* 2,5 Dimethoxy benzaldehyde (332 mg, 2 mmol) and 1,4-bis (3-aminopropyl) piperazine (0.20 ml, 1 mmol) were taken together and grinded for 30 min in a small pastel mortar. Solid product so obtained was crystallized from chloroform to give pure product **5d**.

Grinding by hand at room temperature, solvent for TLC $CHCl_3$/MeOH (9.2:0.8), Yield (83%), mp 100°C, IR (KBr) ν_{max}: 1628 (–C=N–), 1499 and 1464 (Ar) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.875–1.932 (m, 4H, 2 × CH_2), 2.346–2.518 (m, 12H, 6 × CH_2), 3.643–3.669 (t, 4H, J = 6.5 Hz, 2 × CH_2), 3.817 (s, 6H, 2 × OCH_3), 3.834 (s, 6H, 2 × OCH_3), 6.852–6.870 (d, 2H, J = 9 Hz, Ar), 6.940–6.964 (dd, 2H, J = 3 Hz, 6 Hz, Ar), 7.429–7.486 (d, 2H, J = 3.5 Hz, Ar), 8.643 (s, 2H, 2 × –CH=) ^{13}C NMR (125 MHz, DMSO-d_6) δ: 27.6 (C), 52.8 (C), 55.3 (C), 55.5 (C), 56.1 (C), 58.9 (C), 110.2 (C), 113.3 (C), 117.9 (C), 124.4 (C), 152.7 (C), 153.1 (C) and 155.8 (C) GC–MS *m/z* 496 (M^+, 0.50%) Anal. calcd. For $C_{28}H_{40}N_4O_4$ C 67.74; H 8.06; N 11.29 Found C 67.95; H 8.31; N 11.01.

*N^3, N^5-bis (furan-2-yl methylene)-1H-1,2,4-triazole-3,5-diamine (**5e**)* Grinding by hand at room temperature, solvent for TLC $CHCl_3$/MeOH (9.5:0.5), Yield 77%, mp 180–182°C, IR (KBr) ν_{max}: 3321 (NH), 1658 (–C=N–), 1596 and 1515 (Ar) cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 6.725 (s, 2H, Ar), 7.221 (s, 2H, Ar), 7.969 (s, 2H, Ar), 8.762 (s, 2H, 2 × CH=), 11.967 (s, 1H, NH, exch) ^{13}C NMR (125 MHz, DMSO-d_6) δ: 25.1 (C), 66.9 (C), 112.7 (C), 112.9 (C), 113.1 (C), 117.8 (C), 146.8 (C), 148.7 (C), 149.2 (C), 151.1 (C) and 151.7 (C) GC–MS *m/z* 255 (M^+, 4.67%) Anal. calcd. For $C_{12}H_9N_5O_2$ C 56.47; H 3.52; N 27.45 Found C 56.50; H 3.60; N 27.52.

*Furan-2-yl methylene-[3-(4-(3-(furan-2-yl methylene) amino) propyl)-piperazin-1-yl) propyl] amine (**5f**)* Grinding by hand at room temperature, solvent for TLC $CHCl_3$/MeOH (9.2:0.8), Yield 87%, liquid, IR (KBr) ν_{max}: 1634 (–C=N–), 1442 (Ar) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.884–1.942 (m, 4H, 2 × CH_2), 2.374–2.490 (m, 12H, 6 × CH_2), 3.608–3.635 (t, 4H, J = 6.5 Hz, 2 × CH_2), 6.477–6.487 (q, 2H, J = 2 Hz, 3.5 Hz, Ar), 6.734–6.741 (d, 2H, J = 3.5 Hz, Ar), 7.520 (d, 2H, J = 1 Hz, Ar), 8.099 (s, 2H, 2 × –CH=) ^{13}C NMR (125 MHz, DMSO-d_6) δ: 27.3 (C), 52.4(C), 55.2 (C), 58.3 (C), 78.8 (C), 99.5 (C), 111.4 (C), 112.5 (C), 113.3 (C), 144.6 (C), 148.8 (C), 149.3 (C), 151.0 (C), 152.1 (C) and 177.9 (C) Anal. calcd. For $C_{20}H_{28}N_4O_2$ C 67.41; H 7.86; N 15.73 Found C 67.50; H 8.03; N 15.80.

Pharmacology

Anti-inflammatory activity (Winter et al., 1962)

Paw oedema inhibition test was used on albino rats of Charles Foster adopting the method of Winter *et al.*, (1962). Group of five animals of both sexes (body weight 120–160 g), excluding pregnant females, were given a dose of test compound. Thirty minutes later, 0.20 ml of 1% freshly prepared carrageenan suspension in 0.9% NaCl solution was injected subcutaneously into the planter aponeurosis of the hind paw, and the volume was measured by a water plethysmometer apparatus and then measured again 1–3 h later.

The mean increase of paw volume at each interval was compared with that of control group (five rats treated with carrageenan but not with test compound) at the same intervals, and percent inhibition value calculated by the formula given below.

$$\% \text{ anti - inflamatory activity} = [1 - D_t/D_c] \times 100$$

D_t and D_c are paw volumes of oedema in tested and control groups, respectively.

In vitro cytotoxicity against human cancer cell lines (Skehan et al., 1990; Monks et al., 1991)

The human cancer cell lines produced from National Cancer Institute, Frederick, USA were used in this study. Cells were grown in tissue culture flasks in complete growth medium (RPMI-1640 medium with 2 mM glutamine, pH 7.4 supplemented with 10% foetal bovine serum, 100 μg/ml streptomycin and 100 units/ml Penicillin) in a carbon dioxide incubator (37°C, 5% CO_2, 90% RH). The cells at subconfluent stage were harvested from the flask by treatment with trypsin (0.05% in PBS (pH 7.4) containing 0.02% EDTA). Cells with viability of more than 98%, as determined by trypan blue exclusion, were used for determination of cytotoxicity. The cells suspension of 1×10^5 cells/ml was prepared in complete growth medium. Stock 4×10^{-2} M compound solutions were prepared in DMSO. The stock solutions were serially diluted with complete growth medium containing 50 μg/ml of gentamycin to obtain working test solution of required concentrations.

In vitro cytotoxicity against various human cancer cell lines was determined (Monks *et al.*, 1991) using 96-well tissue culture plates. The 100 μl of cell suspension was added to each well of the 96-well tissue culture plates. The cells were allowed to grow in CO_2 incubator (37°C, 5% CO_2, 90% RH) for 24 h. The test materials in complete growth medium (100 μl) were added after 24 h incubation to the wells containing cell suspension. The plates were further incubated for 48 h (37°C in an atmosphere of 5% CO_2 and 90% relative humidity) in a carbon dioxide incubator after addition of test material, and then the cell growth was stopped by gently layering trichloroacetic acid. (50% TCA, 50 μl) on top of the medium in all the wells. The plates were incubated at 4°C for 1 h to fix the cells attached to the bottom of the wells. The liquid of all the wells was gently pipetted out and discarded. The plates were washed five times with distilled water to remove TCA, growth medium, low molecular weight metabolites, serum proteins, etc. and air-dried. Cell growth was measured by staining with sulphorhodamine B dye (Skehan *et al.*, 1990). The absorbed dye was dissolved in Tris–HCl buffer (100 μl, 0.01 M, pH 10.4), and plates were gently stirred for 10 min using a mechanical stirrer. The optical density (OD) was recorded on ELISA reader at 540 nm.

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