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Synthesis, Characterization, in vitro anticancer and Antioxidant studies of Thiazolidin-4-ones

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ABSTRACT

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Keywords: Thiazolidinone, anticancer activity, antioxidant activity.

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CHEMISTRY RESEARCH A RTICLE

Synthesis, Characterization, In vitro anticancer and Antioxidant studies of Thiazolidin-4-ones

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ABSTRACT

Fifteen new triazolo-thiazolidinones were synthesized by the reaction between Schiff bases and thioglycolic acid using anhydrous zinc chloride as catalyst. The characterization of these compounds was done by various spectral techniques. Evaluation of anticancer activity of randomly selected ten thiazolidin-4-ones was carried out in human breast cancer (MCF-7) cells. The quantified (comet assay) increase in DNA damage suggested that all three thiazolidin-4-ones induced dose dependent fragmentation of chromosomal DNA leading to apoptosis. The thiazolidinones displayed only moderate antioxidant activity in DPPH assay.

Keywords: Thiazolidinone, anticancer activity, antioxidant activity.

1. INTRODUCTION

Breast cancer may be one of the oldest known forms of cancerous tumors in humans. Worldwide, breast cancer is the most common cancer in women, after skin cancer, representing 16 % of all female cancers. The rate is more than twice that of colorectal cancer and cervical cancer and about three times that of lung cancer. Mortality worldwide is 25 % greater than that of lung cancer in women. The incidence of breast cancer in India is on the rise and rapidly becoming the number one cancer in females pushing the cervical cancer to the second spot.

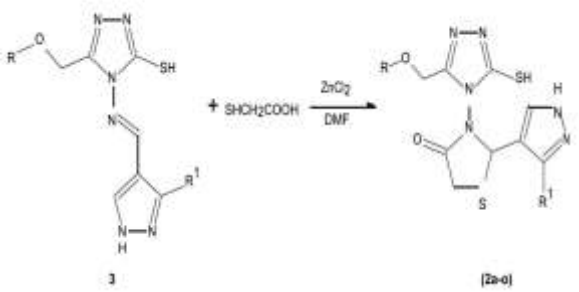
Breast cancer is sometimes treated first with surgery, and then with chemotherapy, radiation, or both. They are given in combinations. One of the most common treatments is Cyclophosphamide plus Doxorubicin; these drugs damage DNA in the cancer, but also in fast-growing normal cells where they cause serious side effects. Damage to the heart muscle is the most dangerous complication of Doxorubicin.

Thiazolidinones are the derivatives of thiazolidine which belong to an important group of heterocyclic compounds containing sulfur and nitrogen in a five member ring. It has been considered as a magic moiety which possesses almost all types of biological activities. The synthesis of compounds belonging to thiazolidinone series constitute an important research area due to their interesting diverse pharmacological activities such as antibacterial, antifungal, anti-inflammatory, antiproliferative, and anticonvulsant properties.

2. MATERIALS USED

General method for the preparation of 2-(3-substituted-1H-pyrazol-4-yl)-3-[3- (substituted) methyl-5-sulfanyl-1, 2, 4-triazol-4-yl]-1, 3- hiazolidin-4-ones (2a- o).

0. 01 mole of substituted Schiff bases 3 and 0.01 mole of thioglycolic acid in DMF were allowed to undergo nucleophilic cycloaddition under reflux in a water bath for 24 h with anhydrous zinc chloride (0.05 g) as catalyst. Excess solvent was removed and the reaction mixture was poured into ice cold water. The solid separated was collected, washed with sodium bicarbonate solution and water. The precipitate of triazolo-thiazolidinone was dried and recrystallized from ethanol. The synthetic route involved in the preparation of triazolo- thiazolidinones is given in Scheme-1.



Comp.No.	R	R1
2a	phenyl	4-chlorophenyl
2b	phenyl	4-fluorophenyl
2c	phenyl	4-anisyl
2d	2-tolyl	4-chlorophenyl
2e	2-tolyl	4-fluorophenyl
2f	2-tolyl	4-anisyl
2g	4-tolyl	4-chlorophenyl
2h	4-tolyl	4-fluorophenyl
2i	4-tolyl	4-anisyl
2j	1-naphthyl	4-chlorophenyl
2k	1-naphthyl	4-fluorophenyl
2l	1-naphthyl	4-anisyl
2m	2-naphthyl	4-chlorophenyl
2n	2-naphthyl	4-fluorophenyl
2o	2-naphthyl	4-anisyl

Scheme-1: Synthetic route for the preparation of thiazolidinones

3. RESULTS AND DISCUSSION

The structures of the newly synthesized compounds were confirmed by spectral data and elemental analysis. And screened for anti-cancer and anti-oxidant evaluation.

SPECTRAL AND ACTIVITY DATA

2-(3-[4-chlorophenyl]-1H-pyrazol-4-yl)-3-(3-phenoxymethyl-5-sulfanyl-1, 2, 4-triazol-4-yl)-1, 3-thiazolidin-4-one (2a)

IR (KBr) [cm-1]: 3500 (pyrazole N-H str.), 3155 (Ar. C-H str.), 1728 (C=O str. of thiazolidinone), 1500 (Ar. C=C str.), 1225 (C-O-C asym. str.), 1090 (C-O-C sym. str.), 608 (>C-S-C< STR.).

1H-NMR (400 MHz, DMSO-d6) [ppm]: δ 5.01 (s, 2H,), δ 5.33 (s, 1H,), δ 5.62 (s, 2H,), δ 7.32 (s, 1H, pyrazole 5-H), δ 7.0-7.8 (m, 9H, Ar.H), δ 7.81 (s, 1H, Pyrazole N-H), δ 13.79 (1H, SH).
MS (m/z): 484 (M+).

2-(3-[4-fluorophenyl]-1H-pyrazol-4-yl)-3-(3-phenoxymethyl-5-sulfanyl-1, 2, 4-triazol-4-yl)-1, 3-thiazolidin-4-one (2b)

IR (KBr) [cm-1]: 3500, 1730 (C=O str.), 1508, 1230, 1092, 605.

1H-NMR (400 MHz, DMSO-d6) [ppm]: δ 5.02 (s, 2H,), δ 5.32 (s, 1H,), δ 5.61 (s, 2H, OCH2), δ 7.33 (s, 1H), δ 7.0-7.8 (m, 9H, Ar.H), δ 7.81 (s, 1H), δ 13.78 (brs, 1H).
MS (m/z): 468 (M+).

2-(3-[4-methoxyphenyl]-1H-pyrazol-4-yl)-3-(3-phenoxymethyl-5-sulfanyl-1, 2, 4-triazol-4-yl)-1, 3-thiazolidin-4-one (2c)

IR (KBr) [cm-1]: 3500, 3150, 2950, 2860, 1729, 1507, 1225, 1098, 610.

1H-NMR (400MHz, DMSO-d6) [ppm]: δ 3.27 (s, 3H, OCH3), δ 5.02 (s, 2H,), δ5.32 (s, 1H,), δ 5.62 (s, 2H, OCH2), δ 7.32 (s, 1H), δ7.0-7.8 (m, 9H, Ar.H), δ 7.82 (s, 1H), δ 13.79 (brs, 1H).
MS (m/z): 480 (M+).

2-(3-[4-chlorophenyl]-1H-pyrazol-4-yl)-3-(3-[2-methylphenoxy] methyl-5-sulfanyl-1, 2, 4-triazol-4-yl)-1, 3-thiazolidin-4-one (2d)

IR (KBr) [cm-1]: 3500, 3150, 2950, 2860, 1733, 1506, 1224, 1098, 608.

1H-NMR (400MHz, DMSO-d6) [ppm]: δ 2.11 (s, 3H, CH3), δ 5.02 (s, 2H,), δ5.33 (s, 1H,), δ 5.61 (s, 2H, OCH2), δ 7.32 (s, 1H), δ7.0-7.8 (m, 8H, Ar.H), δ 7.83 (s, 1H), δ 13.79 (brs, 1H).
MS (m/z): 498(M+).

2-(3-[4-fluorophenyl]-1H-pyrazol-4-yl)-3-(3-[2-methylphenoxy] methyl-5-sulfanyl-1, 2, 4-triazol-4-yl)-1, 3-thiazolidin-4-one (2e)

IR (KBr) [cm-1]: 3500, 3145, 2950, 2862, 1730, 1506, 1228, 1095, 605.
1H-NMR (400 MHz, DMSO-d6) [ppm]: δ 2.12 (s, 3H, CH3), δ 5.02 (s, 2H), δ 5.34 (s, 1H,), δ 5.61 (s, 2H,

OCH2), δ 7.33 (s, 1H), δ7.0-7.8 (m, 8H, Ar.H), δ 7.82 (s, 1H), δ 13.78 (brs, 1H).
MS (m/z): 482(M+).

2-(3-[4-methoxyphenyl]-1H-pyrazol-4-yl)-3-(3-[2-methylphenoxy] methyl-5-sulfanyl-1, 2, 4-triazol-4-yl)-1, 3-thiazolidin-4-one (2f)

IR (KBr) [cm-1]: 3500, 3150, 2940, 2850, 1735, 1509, 1220, 1090, 600.

1H-NMR (400 MHz, DMSO-d6) [ppm]: δ 2.07 (s, 3H, CH3), δ 3.28 (s, 3H, OCH3), δ 5.05 (s, 2H,), δ 5.35 (s, 1H,), δ 5.63 (s, 2H, OCH2), δ 7.35 (s, 1H), δ 6.9-7.8 (m, 8H, Ar.H), δ 7.81 (s, 1H), δ 13.76 (brs, 1H) .
MS (m/z): 494 (M+).

2-(3-[4-chlorophenyl]-1H-pyrazol-4-yl)-3-(3-[4-methylphenoxy] methyl-5-sulfanyl-1, 2, 4-triazol-4-yl)-1, 3-thiazolidin-4-one (2g)

IR (KBr) [cm-1]: 3500, 3147, 2930, 2860, 1727, 1510, 1228, 1091, 610.

1H-NMR (400 MHz, DMSO-d6) [ppm]: δ 2.13 (s, 3H, CH3), δ 5.01 (s, 2H), δ 5.33 (s, 1H,), δ 5.62 (s, 2H, OCH2), δ 7.33 (s, 1H, pyrazole 5-H), δ 7.0-7.8 (m, 8H, Ar.H), δ 7.83 (s, 1H), δ 13.81 (brs, 1H).
MS (m/z): 498(M+).

2-(3-[4-fluorophenyl]-1H-pyrazol-4-yl)-3-(3-[4-methylphenoxy]methyl-5-sulfanyl-1,2,4-triazol-4-yl)-1,3-thiazolidin-4-one (2h)

IR (KBr) [cm-1]: 3500, 3140, 2850, 2930, 1720, 1500 ,1222 ,1097 ,605 .

1H-NMR (400 MHz, DMSO-d6) [ppm]: δ 2.14 (s, 3H, CH3), δ 5.10 (s, 2H), δ 5.37 (s, 1H), δ 5.64 (s, 2H, OCH2), δ 7.35 (s, 1H), δ 7.0-7.8 (m, 8H, Ar.H), δ 7.83 (s, 1H), δ 13.77 (brs, 1H) .
MS (m/z): 482 (M+) .

2-(3-[4-methoxyphenyl]-1H-pyrazol-4-yl)-3-(3-[4-methylphenoxy]methyl-5-sulfanyl-1,2,4-triazol-4-yl)-1,3-thiazolidin-4-one (2i)

IR (KBr) [cm-1]: 3500, 3155 (Ar. C-H str.), 2960, 2850 (methyl C-H str.), 1730 (C=O str), 1505 (Ar. C=C str.), 1230 (C-O-C asym. str.), 1090 (C-O-C sym. str.), 602 (>C-S-C< str.).
1H-NMR (400 MHz, DMSO-d6) [ppm]: δ 2.13 (s, 3H, CH3), δ 3.32 (s, 3H, OCH3), δ 5.08 (s, 2H), δ 5.33 (s, 1H,), δ 5.61 (s, 2H, OCH2), δ 7.32 (s, 1H), δ 7.0-7.8 (m, 8H, Ar.H), δ 7.82 (s, 1H), δ 13.80 (brs, 1H).
MS (m/z): 494 (M+).

2-(3-[4-chlorophenyl]-1H-pyrazol-4-yl)-3-(3-[1-naphthyloxy] methyl-5-sulfanyl-1, 2, 4-triazol- 4-yl)-1, 3-thiazolidin-4-one (2j)

IR (KBr) [cm-1]: 3500, 3152 (Ar. C-H str.), 1732 (C=O str), 1504 (Ar. C=C str.), 1225 (C-O-C asym. str.), 1098 (C-O-C sym. str.), 825 (Ar. C-H def.), 730, 820, 842 (naphthalene C-H def.), 608 (>C-S-C< str.);

1H-NMR (400 MHz, DMSO-d6) [ppm]: δ 5.03 (s, 2H), δ 5.34 (s, 1H), δ 5.62 (s, 2H, OCH2), δ 7.32 (s, 1H), δ 7.0-8.1 (m, 11H, Ar.H), δ 7.80 (s, 1H), δ 13.79 (brs, 1H).
MS (m/z): 534 (M+).

2-(3-[4-fluorophenyl]-1H-pyrazol-4-yl)-3-(3-[1-naphthyloxy] methyl-5-sulfanyl-1, 2, 4-triazol-4-yl)-1, 3-thiazolidin-4-one (2k)

IR (KBr) [cm-1]: 3500, 3155, 1732, 1508, 1238, 1088, 824, 750, 830, 844, 610.

1H-NMR (400 MHz, DMSO-d6) [ppm]: δ 5.04 (s, 2H), δ 5.33 (s, 1H), δ 5.62 (s, 2H, OCH2), δ 7.32 (s,1H, pyrazole 5-H), δ 7.0-8.1 (m, 11H, Ar.H), δ 7.81 (s, 1H), δ 13.78 (brs, 1H).
MS (m/z): 518 (M+).

2-(3-[4-methoxyphenyl]-1H-pyrazol-4-yl)-3-(3-[1-naphthyloxy]methyl-5-sulfanyl-1,2,4-triazol-4-yl)-1,3-thiazolidin-4-one (2l)

IR (KBr) [cm-1]: 3500, 3148,2950, 2860,1733 , 1505, 1232 ,1095, 820 752, 828, 609.

1H-NMR (400 MHz, DMSO-d6) [ppm]: δ 3.29 (s, 3H, OCH3), δ 5.03 (s, 2H), δ 5.32 (s, 1H), δ 5.62 (s, 2H, OCH2), δ 7.33 (s, 1H), δ 7.0-8.1 (m, 11H, Ar.H), δ 7.81 (s, 1H,), δ 13.79 (brs, 1H).
MS (m/z): 530 (M+).

2-(3-[4-chlorophenyl]-1H-pyrazol-4-yl)-3-(3-[2-naphthyloxy]methyl-5-sulfanyl-1,2,4-triazol- 4-yl)-1,3-thiazolidin-4-one (2m)

IR (KBr) [cm-1]: 3500, 3150 (Ar. C-H str.), 1730 (C=O str.), 1507 (Ar. C=C str.), 1230 (C-O-C asym. str.), 1090 (C-O-C sym. str.), 820 (Ar. C-H def.), 750, 820, 840 (naphthalene C-H def.), 606 (>C-S-C< str.).

1H-NMR (400 MHz, DMSO-d6) [ppm]: δ 5.05 (s, 2H), δ 5.35 (s, 1H), δ 5.63 (s, 2H, OCH2), δ 7.33 (s, 1H), δ 7.0-8.1 (m, 11H, Ar.H), δ 7.81 (s, 1H), δ 13.78 (brs, 1H, SH).
MS (m/z): 534(M+).

2-(3-[4-fluorophenyl]-1H-pyrazol-4-yl)-3-(3-[2-naphthyloxy]methyl-5-sulfanyl-1,2,4-triazol-4-yl)-1,3-thiazolidin-4-one (2n)

IR (KBr) [cm-1]: 3500, 3155, 1731 (C=O str.)1504 (Ar. C=C str.), 1234 (Ar. C-O-C asym. str.), 1090 (C-O-C sym. str.), 825 (Ar. C-H def.), 752, 820, 845 (naphthalene C-H def.), 610 (>C-S-C< str.).

1H-NMR (400 MHz, DMSO-d6) [ppm]: δ 5.05 (s, 2H), δ 5.32 (s, 1H), δ 5.63 (s, 2H, OCH2), δ 7.35 (s, 1H, pyrazole 5-H), δ 7.0-8.1 (m, 11H, Ar.H), δ 7.81 (s, 1H, Pyrazole N-H), δ 13.78 (brs, 1H, SH).
MS (m/z): 518 (M+).

2-(3-[4-methoxyphenyl]-1H-pyrazol-4-yl)-3-(3-[2-naphthyloxy]methyl-5-sulfanyl-1,2,4-triazol-4-yl)-1,3-thiazolidin-4-one (2o)

IR (KBr) [cm-1]: 3500, 3150, 2950, 2860, 1733, 1505, 1236, 1095, 820, 752, 825, 846, 608.

1H-NMR (400 MHz, DMSO-d6) [ppm]: δ 3.28 (s, 3H, OCH3), δ 5.04 (s, 2H), δ 5.33 (s, 1H), δ 5.61 (s, 2H, OCH2), δ 7.33 (s, 1H), δ 7.0-8.1 (m, 11H, Ar.H), δ 7.81 (s, 1H, Pyrazole N-H), δ 13.79 (brs, 1H, SH).
MS (m/z): 530 (M+).

(I) In vitro anticancer studies

Evaluation of anticancer activity of randomly selected ten thiazolidin-4-ones was carried out in human breast cancer (MCF-7) cells. The MCF-7 cells were purchased from National Cancer Center for Cell Science, Pune, India.

(i) MTT assay

The stock solution of thiazolidin-4-ones to determine their cytotoxic effect were prepared in 10 % DMSO and further diluted in PBS before use. The final concentration of DMSO in the solution was less than 0.1 %. The results were reported as percentage survival of the cells when compared to that of the untreated control cells ± standard deviation in Table 1. The IC50 for the standard drug Doxorubicin (DOX) was found to be 18 µg/mL. Among the ten new thiazolidin-4-ones screened for cytotoxicity in MTT assay, 2b, 2d and 2f exhibited cytotoxicity with IC50 values of 30, 22 and 29 µg/mL respectively. The methyl group in the ortho position of phenyl group probably might have augmented the activity of 2d and 2f. 2j, 2l and 2m with the bulky naphthyl groups displayed least cytotoxic activity.

Table 1: MTT assay of thiazolidin-4-ones

Comp No.	Vehicle Control	0.1 µg/mL	1 µg/mL	10 µg/mL	100 µg/mL	IC_{50} µg /mL
2b	100 ± 5.99	65.92 ± 4.74	69.43 ± 8.41	76.47 ± 4.65	33.60 ± 1.77	30
2c	100 ± 7.53	100 ± 10.45	100 ± 5.10	96.80 ± 1.8	46.45 ± 6.5	85
2d	100 ± 5.90	70.0 ± 4.60	80.7 ± 5.0	67.57 ± 3.4	13.2 ± 1.40	22
2e	100 ± 5.90	81.4 ± 6.20	83.1 ± 4.6	92.5 ± 5.70	62.1 ± 8.40	> 100
2f	100 ± 7.50	81.5 ± 10.4	87.0 ± 5.4	84.7 ± 1.7	25.4 ± 1.80	29
2h	100 ± 5.99	80.84 ± 2.6	74.66 ± 4.7	87.5 ± 8.50	71.4 ± 8.70	> 100
2i	100 ± 5.90	95.05 ± 4.8	95.38 ± 9.2	90.2 ± 5.20	43.67 ± 5.5	78
2j	100 ± 2.09	100 ± 2.10	70.5 ± 3.7	60.3 ± 7.90	51.8 ± 1.30	100
2m	100 ± 7.50	99.7 ± 10.2	100 ± 3.69	81.4 ± 3.08	50.7 ± 4.30	100
2n	100 ± 7.50	100 ± 7.50	100 ± 3.59	99.85 ± 2.54	96.5 ± 5.40	> 100

(ii) Comet assay

The images of comet assay for control, cells treated with Doxorubicin (0.1 µM, 54 µg/mL), 2b (50 µg/mL), 2d (50 µg/mL) and 2f (50 µg/mL) are shown in Fig.1. In the comet assay, the images of cells treated with DOX, 2b, 2d and 2f showed the formation of comets. No comet pattern was observed in the control cells. There was dose dependent increase in tail length and olive tail moment when treated with 2b, 2d and 2f. 2d presented maximum apoptotic DNA damage among the three thiazolidin-4-ones studied, which was in accordance with its maximum cytotoxicity as seen in MTT assay. None of the thiazolidin-4-ones exhibited apoptotic DNA damage to the extent of DOX. The results of the assay for tail length and olive tail moment are shown in Fig. 1. & Fig. 2 respectively.

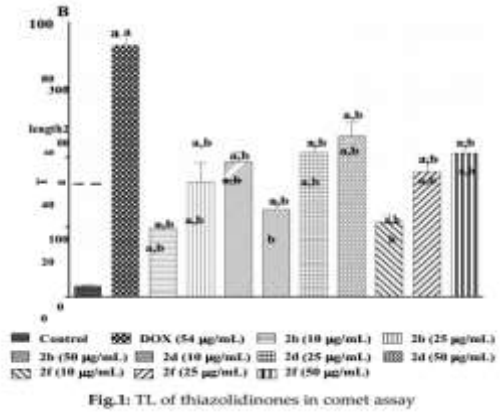


Fig.1: TL of thiazolidinones in comet assay

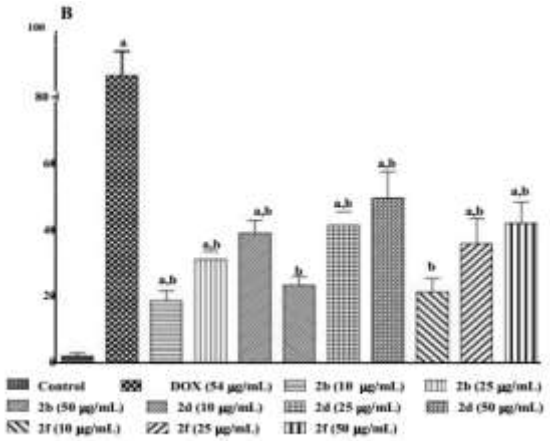


Fig.2: OTM of thiazolidinones in comet assay

(II) In vitro antioxidant studies

(i) DPPH radical scavenging assay

The ability of 2b, 2d and 2f to scavenge DPPH radical in various concentrations was studied. Experiment was performed in triplicates and average values were considered. Results of the DPPH assay are shown in Table 2. Thiazolidinones were found to be moderately active in DPPH assay. Among the three thiazolidinones studied, 2b showed maximum antioxidant behavior.

Table2: Antioxidant activity data of thiazolidin-4-ones

Comp. No.	IC_{50} (µg/mL)	
	DPPH	ABTS
Ascorbic Acid	18.74 ± 1.16	31.53 ± 2.85
2b	27.16 ± 2.15	143.67 ± 5.70
2d	31.52 ± 1.97	73.03 ± 3.90
2f	46.95 ± 2.42	165.78 ± 6.44

(ii) ABTS radical scavenging assay

The electron transfer capability of 2b, 2d and 2f was studied using ABTS radical scavenging assay. The experiment was performed in triplicates and average values were considered. The results of ABTS assay is shown in Table 2. None of the three thiazolidinones were as active as the standard, Ascorbic acid.

4. CONCLUSION

Fifteen new triazolo-thiazolidinones were synthesized by the reaction between Schiff bases and thioglycolic acid using anhydrous zinc chloride as catalyst. The characterization of these compounds was done by various spectral techniques. 2-(3-[4-chlorophenyl]-1H- pyrazol-4-yl)-3-(3-[2-methylphenoxy]methyl-5-sulfanyl-1,2,4-triazol-4-yl)-1,3-thiazolidin-4-one (2d) was the most cytotoxic among all the ten thiazolidinones screened for anticancer behaviour. The mode of cell death through apoptosis was confirmed by comet assay. There was a concentration dependent increase in tail length and olive tail moment in the comet assay. The chlorine atom might have added to the potency of thiazolidinone 2d as it produces simultaneously an increase in lipophilicity and an electron attracting effect. The presence of chlorine atoms might have also favored the passage of biomembranes. The steric hindrance created by methyl group at the ortho position of phenyl ring could have created constraints and hence forced the molecule to attain certain conformations that might have favored interactions with the target receptors, thereby increasing the activity of 2d.

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