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ARTICLE TYPE

α-Aminophosphonates as novel antileishmanial chemotypes: synthesis, biological evaluation, and CoMFA studies

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Abstract: A series of twenty six structurally diverse α-aminophosphonates have been synthesized and evaluated for *in vitro* antileishmanial activity and cytotoxicity using MTT assay. Among them, seven compounds (1-7) exhibited antileishmanial potency against *L. donovani* promastigote with IC_{50} values in the low micromolar range. The structure activity relationship was quantitatively evaluated by a statistically reliable CoMFA model with high predictive abilities (r^2_{pred} = 0.87, r^2_{ncv} = 0.985).

1. Introduction

Leishmaniasis, a parasitic disease causes a major public health problem, prevailed in some tropical and sub-tropical areas of the world. One of its types, visceral leishmaniasis (VL), also known as kala-azar, is highly endemic in the Indian subcontinent and in East Africa. The majority of VL cases occur in Bangladesh, Brazil, Ethiopia, India, Nepal, and Sudan.[1] It is transmitted by the bite of infected female phlebotomine sand-fly belonging to the genus Leishmania. Leishmaniasis affects an estimated 350 million people worldwide with 1.5-2 million new cases and 70,000 deaths each year.[2] The existing chemotherapies are not effective enough as these have various drawbacks such as significant toxicity, variable efficacy, lack of oral bioavailability, and high cost involved during the treatment. The development of resistance against the available therapeutics is another major bottleneck in treating the disease condition with the compounded problem of Leishmania-HIV co-infections. The pentavalent antimonials, that remained the first line therapeutic options for more than 50 years,[3] have the potential side effects causing acute pancreatitis and cardiac arrhythmia leading to death in extreme cases[4] and have exhibited large scale clinical resistance including in India.[5] The second line drugs pentamidine and amphotericin B are not active orally, need long term treatment and may lead to renal, pancreatic, and hepatic toxicity, hypotension, and dysglycemia.[6] Amphotericin B triggers hypokalemia and nephrotoxicity as the most common side effects apart from the life-threatening first-dose anaphylaxis. Thus, for the global health programs there has been a pressing need for the discovery of new lead compounds for the treatment of leishmaniasis.[7] The phospholipids (Figure 1), originally discovered as anti-cancer drugs, have emerged as a new class of anti-protozoal/parasitic agents[8] and the analogue miltefosine (**1a**) has been registered as the first oral drug for the treatment of the disease in India in 1992[7g,9] and in Colombia in 2005.[10] Other phospholipid analogues as promising drug candidates are edelfosine (**1b**) and elmofosine (**1c**).[11] However, **1a** has long half-life (6-8 days) in humans and low therapeutic ratio that are conducive to the development of resistance and it is not suitable for pregnant women as it has potential teratogenic effect and shows severe gastrointestinal side effects[12] and unsatisfactory results for treating HIV co-infected patients.[13] These have directed efforts towards the development of antileishmanial phospholipids[14] with an aim to deriving more efficacious drug candidates. We were attracted by the remarkable potential of the α-aminophosphonate structural motif in medicinal chemistry due to diverse biological activities[15] and report herein α-aminophosphonates as novel antileishmanial chemotypes.

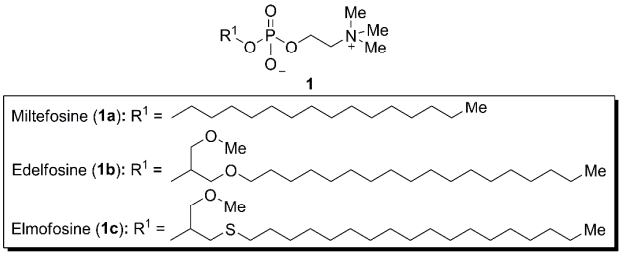


Figure 1. Phospholipids as newly emerged antileishmanials.

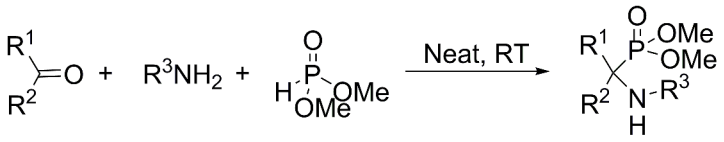
2. Results and discussion

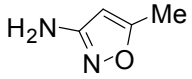
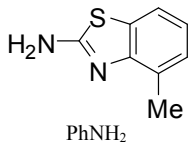
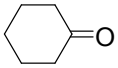
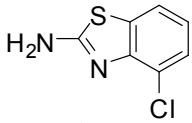
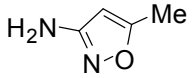
Chemistry

α-Aminophosphonates can be prepared through a three component reaction involving aldehydes/ketones, amines, and phosphites (Kabachnik-Fields reaction)[16] usually performed under the presence of suitable Lewis acid catalysts.[17] In the present study a catalyst and solvent-free protocol under room temperature operation was developed (Table 1).[18] In most of the cases the reactions took place efficiently affording the desired α-aminophosphonates in very good yields in 3-6 h. In a few cases where the product conversion was poor, the reactions were performed in the presence of anhydrous

$Mg(ClO_4)_2$ (5 mol %)[17b] either at rt (entry 11) or at 80 °C (entries 3,4,9,14,18) to afford the desired product in improved yields. A total twenty six structurally diverse α-aminophosphonates were synthesized which are stable at room temperature.

Table 1. One pot three component reaction for the synthesis of diverse α-aminophosphonates and their biological activities.



Code	R^1	R^2	R^3NH_2	Time (h)	Yield[b] (%)	IC_{50}[e] (μM)	CC_{50}[f] (μM)	SI[g] (CC_{50}/IC_{50})
1	4-(OH), 3-(OMe)-C_6H_3	H	$PhNH_2$	6	88	7.1(±0.14)	5	0.70
2	4-(OH)-C_6H_4	H	$PhNH_2$	6	86	8(±0.14)	6.5	0.81
3	4-(OMe)-C_6H_4	H		4	78[c]	8(±2.9)	7.5	0.94
4	4-(OMe)-C_6H_4	H		5	76[c]	8.75(±3)	8.5	0.97
5	4-(NO2)-C_6H_4	H	$PhNH_2$	6	83	8.95(±0.95)	5	0.56
6	2-(OH)-C_6H_4	H	$PhNH_2$	7	88	8.95(±0.05)	5	0.56
7	3-(OH), 4-(OMe)- C_6H_3	H	$PhNH_2$	6	86	9.75(±0.125)	31	3.18
8	Ph	H	$PhNH_2$	3	94	13.5(±5)	12.5	0.93
9	Ph	Me	$PhNH_2$	6	77[c]	13.5(±1.5)	6	0.44
10	3,5-di-(OMe),4-(OH)-C_6H_2	H	$PhNH_2$	6	79	13.5(±7.7)	10	0.74
11		-	$PhNH_2$	6	91[d]	16.4(±1.6)	7.5	0.46
12	Ph-CH=CH	H	$PhNH_2$	4	87	17.5(±2.5)	8	0.46
13	2-(OMe)-C_6H_4	H	$PhNH_2$	6	89	18(±2)	6	0.33
14	4-(OMe)-C_6H_4	H		4	77[c]	22	-	-
15	2-(Br)-C_6H_4	H	$PhNH_2$	6	82	22.5(±1.5)	5.5	0.24
16	2-(F)-C_6H_4	H	$PhNH_2$	4	91	24(±2)	12	0.50
17	4-(OMe)-C_6H_4	H	$PhNH_2$	4	91	25(±1.4)	5.5	0.22
18	Ph	H		2	76[c]	30	-	-
19	4-(Cl)-C_6H_4	H	$PhNH_2$	4	92	36(±4)	39	1.08
20	4-(Br)- C_6H_4	H	$PhNH_2$	6	81	39(±1)	6.5	0.17
21	1-Naphthyl	H	$PhNH_2$	4	83	56(±4)	>100	-
22	2-Pyridyl	H	$PhNH_2$	6	81	90	5	0.06
23	2-Naphthyl	H	$PhNH_2$	4	85	91.5(±1.5)	6.1	0.07
24	Cyclohexyl	H	$PhNH_2$	4.5	81	>100	14	-
25	4-(NMe_2)-C_6H_4	H	$PhNH_2$	3.5	93	>100	5	-
26	3-(OH)-C_6H_4	H	$PhNH_2$	5	82	>100	>100	-
Std	Amphotericin B	-	-	-	-	0.405(±0.015)	7	17.28

[a]The mixture of the carbonyl compound (1 mmol), amine (1 mmol), and alkyl phosphite (1.2 mmol) was stirred magnetically at room temperature (~25-30 °C) under neat condition for specified time. [b]Yield of the corresponding α-aminophosphonate after isolation and purification (^{1}H NMR and MS). [c]The reaction was performed in the presence of anh $Mg(ClO_4)_2$ (5 mol%) under neat condition at 80 °C (oil bath). [d]The reaction was performed in the presence of anh $Mg(ClO_4)_2$ (5 mol%) under neat condition at room temperature (~25-30 °C).[e]IC_{50}: Concentration of compound inhibiting 50% of the parasite growth. [f]CC_{50}: 50% reduction in the viability of the cells after treatment with the drug in comparison to the control. [g]SI: CC_{50} value/IC_{50} value.

2.1. *Biology*

The antileishmanial activity of the synthesized α-aminophosphonate (**1-26**) was evaluated against the extracellular promastigote stage of *L. Donovani* (MHOM/80/IN/Dd8) using (4, 5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay.[19] Amphotericin B was employed as the positive control. The IC_{50} values of the post treated viable cells were calculated relative to the untreated control cells and the results were expressed as the concentration of the compound inhibiting 50% of the parasite growth.

The IC_{50} values of **1-26** as well as of the standard drug amphotericin B are provided in Table 1. Out of these twenty six compounds, seven compounds (**1-7**) showed antileishmanial activity in the range 7-10 μM and five compounds (**8-13**) showed moderate activity between 10-20 μM.[20] All of these compounds and amphotericin B were also tested for *in vitro* cytotoxicity against J774A-1 macrophage cell line by MTT assay.[19] The cytotoxicity was expressed as CC_{50} *i.e.* 50 % reduction in the viability of the cells after treatment with the drugs in comparison to the control and the results are shown in Table 1. In general, these compounds exhibited low SI but their cytotoxicity in J774A-1 macrophages are comparative to that of the reference drug amphotericin B.

2.2. *3D-QSAR analysis*

The Comperative Molecular Field Analysis (CoMFA), a 3D-QSAR method, is widely used for quantitatively establishing the structure activity relationship.[21] Thus, CoMFA was applied to identify the structural features essential for anti-leishmanial activity of the α-aminophosphonates. The stereochemistry (active conformation) plays key role in CoMFA analysis. However, the lowest energy conformation is not always the active conformation. As the compounds were synthesized in the racemic form and the antileishmanial acitivity was determined as such, in the absence of experimental data on the biologically relevant active conformation (for example, atomic coordinates from X-ray crystallographic studies of the ligand-receptor complex), we resorted to test both the (*R*)- and (*S*)- stereoisomers independently.

The (*S*)-isomer generated the lowest minimum energy state calculated using SYBYL 7.1 molecular modeling package[22] than the (*R*) form. Similar challenges faced by other research groups have identified lowest energy conformation generated by designing CoMFA model of the individual stereoisomers and was subsequently found to correlate well with the preferable bioactive conformation based on the crystal structure and was in conformity with the derived biological activity.[23] To better understand the contribution of the activity of these compounds, both of the (*R*)- and (*S*)- forms were used to build the model using SYBYL 7.1 (Tripos Inc., USA) molecular modeling package.[22] The alignment of all the compounds with (*S*)-form as the lowest energy state is provided in Figure 2. The statistically reliable CoMFA model was developed and validated by PLS method. The statistical parameters of the two models derived from the (*R*) - and (*S*) - stereoisomers are summarized in Table 2.

The CoMFA results suggest that the model using the (*S*) form has accepted predictive ability ($r^2_{pred} > 5$) whereas that using the (*R*) - isomer does not meet the prediction standard. The model derived from the (*S*) form is superior to the counter model in all expects such as low standard error, higher cross validated and non-cross validated values. This model was further validated by the test set method. All compounds were predicted within acceptable range using the model derived with the (*S*) form. The scattered plots of experimental pIC_{50} against the predicted pIC_{50} value of the training set and test set is shown in Figure 4. These results suggest that the model is reliable and it could serve as a useful tool for predicting the IC_{50} values of novel α-aminophosphonates.

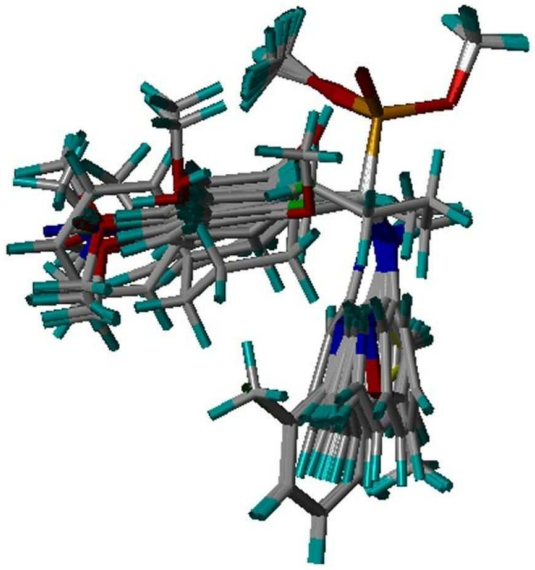


Figure 2. Alignment of all molecules used for CoMFA molecular field generation.

Table 2. Statistical Results of CoMFA Model.

Confor-mation	r^2_{cv} [a]	r^2_{ncv} [b]	SEE[c]	ONC[d]	F[e]	r^2_{pred} [f]	Field contribution	
							Steric	Electro-static
S	0.589	0.986	0.182	5	194	0.87	47.7	52.3
R	0.190	0.972	0.237	6	91.7	0.43	57.2	42.8

[a] Leave one out (LOO) cross-validated correlation coefficient, [b] no validation correlation coefficient, [c] Standard Error of Estimate, [d] Optimal number of components, [e] F test value, [f] Predictive correlation coefficient.

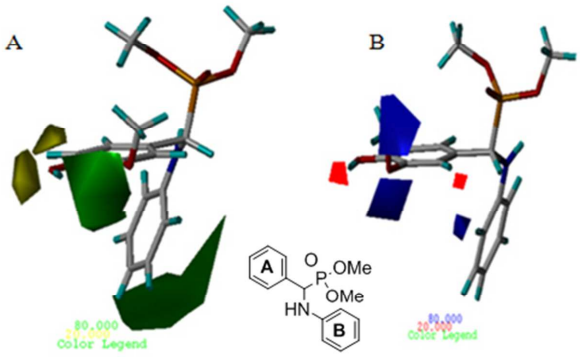


Figure 3. CoMFA contour maps for α-aminophosphonates: (A) steric field, (B) electrostatic field distribution around highly active compound **1**.

The contour map analysis was performed to study the effect of the substituent on the anti-leishmanial activity. The steric and electrostatic contribution for best CoMFA model was found to be 47.7 and 52.3%, respectively. The green and yellow colour (80 and 20% contributions) contour maps show the favorable and unfavorable steric interactions, respectively.

Figure 3A shows the distribution of steric fields generated around the most potent compound **1**. A green contour was sighted around the third (*meta*) position of the phenyl ring (Ring **A**) indicating the favorable region for the presence of a bulky group. Phenyl ring with 3-methoxy substituent such as in **1** increases the activity (7.1 μM) whereas the 3-hydroxyl substituent alone as in **26** resulted in loss of activity (>100 μM). Another big green plot is stretched around the 3', 4' position of the amino phenyl ring (Ring **B**). Replacement of the phenyl ring of the α-aminophenyl group by the heterocyclic ring (**3**, **4**) favors activity. One yellow region is sighted in the steric contour map at the fourth and fifth position of the phenyl ring A suggesting that bulky group in this region disfavors the antileishmanial activity. The SAR data suggest that the moderate activity of **17** with the *para* methoxy substituent and complete loss of activity of **25** due to the *N*, *N*–dimethylamino substituent (>100 μM) may be due to interaction of the OMe and the NMe_2 group in the unfavorable yellow contour.

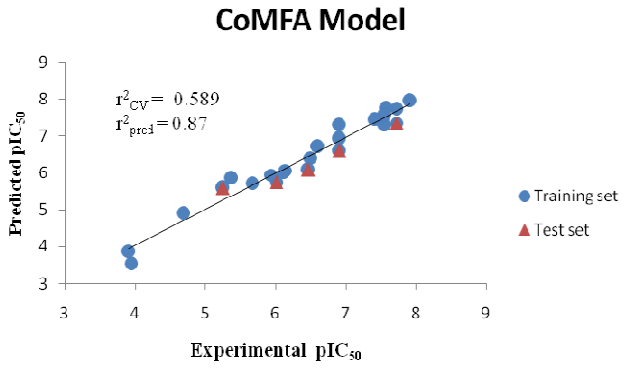


Figure 4. Plot of experimental pIC_{50} versus predicted pIC^{50} values for the 3D-QSAR/CoMFA model.

Table 3. Experimental and CoMFA-predicted pIC_{50} values of molecules in both training set and test set

Code	Experimental Activity		Rescaled	Predicted	δ
	IC_{50}(μM)	pIC_{50}	pIC_{50}	pIC_{50}	
1	7.1(±0.14)	5.15	7.91	7.95	-0.04
2	8(±0.14)	5.10	7.72	7.75	-0.03
3*	8(±2.9)	5.10	7.72	7.36	0.36
4	8.75(±3)	5.06	7.58	7.77	-0.19
5	8.95(±0.95)	5.05	7.55	7.31	0.24
6	8.95(±0.05)	5.05	7.55	7.56	-0.01
7	9.75(±0.125)	5.01	7.42	7.44	-0.02
8	13.5(±5)	4.87	6.91	7.29	-0.38
9*	13.5(±1.5)	4.87	6.91	6.59	0.32
10	13.5(±7.7)	4.87	6.91	6.93	-0.02
11	16.4(±1.6)	4.79	6.60	6.71	-0.11
12	17.5(±2.5)	4.76	6.50	6.41	0.09
13*	18(±2)	4.74	6.46	6.08	0.38
14	22	4.66	6.14	6.07	0.07
15	22.5(±1.5)	4.65	6.11	6.02	0.09
16*	24(±2)	4.62	6.01	5.75	0.26
17	25(1.4)	4.60	5.94	5.95	-0.01
18	30	4.52	5.66	5.73	-0.07
19	36(±4)	4.44	5.37	5.87	-0.5
20*	39(±1)	4.41	5.25	5.59	-0.34
21	56(±4)	4.25	4.68	4.93	-0.25
22	90	4.05	3.94	3.53	0.41
23	91.5(±1.5)	4.04	3.91	3.88	0.03

*Test Set

Figure 3B shows the contribution of the electrostatic fields generated around the most potent compound **1.** Blue and red colour (80% and 20% contributions) contour maps show the favorable and unfavorable electrostatic interactions, respectively. Two red contours were sighted in close proximity to the *ortho* and *para* position of the phenyl ring A. The red contour indicates that electronegative group at the *ortho* and *para* position augments the antileishmanial activity. As seen in SAR, the most active compound contains either hydroxyl (**1**) (7.1 μM) or nitro (**5**) (8.95 μM) group at the *para* position, while a molecule possessing electropositive group (**25**) at the same position resulted in the decreased activity (>100 μM). Similarly, substitution of the electronegative hydroxyl group (**6**) (8.95 μM) at the *ortho* position of the phenyl ring by the electropositive methoxy group (**13**) (18 μM) or nitrogen of the pyridine ring (**22**) (90 μM) results in decreased activity. Two blue contour plots covering the *meta* position of the phenyl ring A and the *ortho*

position of the α-amino phenyl ring B indicates that the electropositive potential of the ring favors the activity. This has been observed with the molecules containing electropositive methoxy group at the third (*meta*) position of phenyl ring A and nitrogen on the hetero rings like isoxazole (**3**) and benzothiazole (**4**, **14**). Presence of electronegative hydroxyl group (**26**) at the electropositive *meta* position of phenyl ring results in decreased activity (>100 μM). Overall the SAR of the α-aminophosphonate series suggests that replacement of aromatic phenyl ring (**8**) by hetero pyridine ring (**22**) or cyclohexane ring (**24**) results in decreased activity. Substitution of the phenyl ring by the bicyclic naphthalene ring (**21, 23**) resulted in the moderate to low activity.

3. Conclusion

α-Aminophosphonates are found to be novel antileishmanial chemotypes. The structurally diverse α-aminophosphonates were synthesized following a modified Kabachnik-Field reaction performed under solvent and catalyst-free conditions at room temperature. Twenty six α-aminophosphonates were subjected to the *in vitro* evaluation for antileshmanial activity against *L. donovani* promastigotes using MTT assay. Seven compounds displayed potent inhibitory activity in low (7.1-9.75) μM range. These compounds exhibited cytotoxicity (against J774A-1 macrophages) profile similar to that of the standard drug Amphotericin B. To establish the 3D structure activity relationship, CoMFA models were derived using the (*R*)- and (*S*)- stereoisomeric/enantiomeric forms of the α-aminophosphonate and the (*S*)- form generated the best predictive model. The CoMFA model generated based on the obtained biological data provides inference that there is further scope of modifying Ring A with electronegative substituent at *para* position and bulky electropositive substituent at *meta* position. Present study suggests that substitution of ring B with various substituted heterocyclic rings could provide future scope for further exploring α-aminophosphonate class of compounds as potential antileishmanial agent.

Notes and references

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† Electronic Supplementary Information (ESI) available: [Procedure for the synthesis, molecular modelling, spectral characterization and biological evaluation is described]. See DOI: 10.1039/b000000x/

1. (a) World Health Organization, Leishmaniasis report 2012 http://www.who.int/leishmaniasis/burden/en/ (b) F. Chappuis, S. Sundar, A. Hailu, H. Ghalib, S. Rijal, R.W. Peeling, J. Alvar and M. Boelaert, *Nat. Rev. Microb.* 2007, **5**, 873-882.
2. P. Desjeux, *Comp. Immunol. Microb*. 2004, **27**, 305-318.
3. (a) S. L Croft and V. Yardley, *Curr. Pharm. Des.* 2002, **8**, 319-342. (b) J. D. Berman *Clin. Infect. Dis*. 1997, **24**, 684-703.
4. H. W. Murray, J. D. Berman, C. R. Davies and N. G. Saravia, *Lancet* 2005, **366**, 1561-1577.
5. (a) F. Faraut-Gambarelli, R. Piarroux, M. Deniau, B. Giusiano, P. Marty, G. Michel, B. Faugère and H. Dumon, *Antimicrob. Agents Chemother*. 1997, **41**, 827-830. (b) R. Lira, S. Sundar, A. Makharia, R. Kenney, A. Gam, E. Saraiva and D. Sacks, *J. Infect. Dis.,* 1999**, 180**, 564–567. (c) S. Sundar, *Trop. Med. Inter. Health*, 2001, **6,** 849–854.
6. N. R. Poola, M. Kalis, F. M. Plakogiannis and D. R. J. Traft, *J. Antimicrob. Chemother*. 2003, **52,** 397-404.
7. (a) T. Kobes, I. Grekov and M. Lipoldová, *Curr. Med. Chem*. 2012, **19**, 1443-1474. (b) L. H. Freitas-Junior, E. Chatelain, H. A. Kim and J. L. Siqueira-Neto, *Int. J. Parasitol.: Drugs Drug Resist.* 2012, **2**, 11–19. (c) S. L. Croft and P. Olliaro, *Clin. Microbiol. Infect.* 2011, **17**, 1478–1483. (d) A. Cavalli and M. L. Bolognesi, *J. Med. Chem.* 2009, **52**, 7339–7359. (e) S. L. Croft, K. Seifert and V. Yardley, *Ind. J. Med. Res*. 2006, **123**, 399-410. (f) S. Sundar and M. Chatterjee, *Ind. J. Med. Res*. 2006, **123**, 345-352. (g) S. L. Croft, M. P. Barrett and J. A. Urbina, *Trends Parasitol*. **2005**, 21, 508-512. (h) S. L Croft and G. H. Coombs, *Trends Parasitol.* 2003, **19**, 502-508
8. (a) S. L. Croft, D. Snowdon and V. J. Yardley, *Antimicrob. Chemother*. 1996, **38**, 1041-1047. (b) S. L. Croft, K. Seifert and M. Duchêne *Mol. Biochem. Parasitol*. 2003, **126**, 165-172.
9. J. J. Berman, *Expert Opin. Drug Metab. Toxicol*. 2008, **4,** 1209-1216.
10. J. Soto, *Expert Rev. Anti Infect. Ther*. 2006, **4,** 177- 185.
11. (a) S. Azzouz, M. Maache, R. G. Garcia and A. Osuna, *Basic Clin. Pharmacol. Toxicol.* 2005*,* **96***,* 60–65. (b) R. E. Varela-M, J. A. Villa-Pulgarin, E. Yepes, I. Müller, M. Modolell, D. L. Muñoz, S. M. Robledo, C. E. Muskus, J. López-Abán, A. Muro, I. D. Vélez and F. Mollinedo,. *PLoS Negl. Trop. Dis.* 2012, **6: e1612**, 1-14.
12. (a) B. L. Herwaldt, *N. Engl. J. Med.* 1999, **341**, 1840-1842. (b) J. D. Berman, *Mini Rev. Med. Chem.* 2006, **6**, 145-151.
13. H. Sindermann, K. R. Engel, C. Fischer and W. Bommer, *Clin. Infect. Dis.* 2004, **39**, 1520-1523.
14. (a) I. Papanastasiou, K. C. Prousis, K. Georgikopoulou, T. Pavlidis, E. Scoulica, N. Kolocouris and T. Calogeropoulou, *Bioorg. Med. Chem. Lett*. 2010, **20**, 5484–5487. (b) K. Seifert, A. Lemke, S. L. Croft and O. Kayser *Antimicrob. Agents Chemother*. 2007, **51**, 4525–4528.
15. Reviews: (a) J. Galezowskaa and E. Gumienna-Kontecka, *Coord. Chem. Rev.* 2012, **256**, 105–124. (b) A. Mucha, P. Kafarski and Berlicki, Y. *J. Med. Chem.* 2011, **54**, 5955-5980. Recent reports on biological activities: (c) A. K. Bhattacharya, K. C. Rana, C. Pannecouque and E. De Clercq, *ChemMedChem,* 2012, **7**, 1601-1611. (d) F. Mohamed, Abdel-Megeed, A. Gamal, El-Hiti, B. E. Badr, M. M. Azaam, *Phos. Sul. Sil. Rel. Elem.* 2013, **188**, 879-885. (e) C. Sampath, K. V. Vani, Y. Kotaiah, N. H. Krishna, C. N. Raju and C. Venkata Rao, *J. Chem. Pharm. Res.* 2012, **4**, 1375-1382. (f) Z. Rezaei, S. Khabnadideh, K. Zomorodian, K. Pakshir, S. Nadali, N. Mohtashami and E. F. Mirzaei, *Int. J. Med. Chem.* 2011, **2011** (678101), 11. (g) S. A. Dake , D. S. Raut, K. R. Kharat, R. S. Mhaske, S. U. Deshmukh and R. P. Pawar *Bioorg. Med. Chem. Lett*., 2011, **21**, 2527-2532.
16. (a) M. I. Kabachnik and T. Y. Medved', *Dokl. Akad. Nauk SSSR* 1952, **83**, 689-691; Chem. Abstr. 1953, **47**, 2724b. (b) E. K. Fields, *J. Am. Chem. Soc.* 1952, **74**, 1528-1531.
17. (a) S. Bhagat and A. K. Chakraborti. *J. Org. Chem.* 2008, **73**, 6029-6032. (b) S. Bhagat and A. K. Chakraborti, *J. Org. Chem.* 2007, **72**, 1263-1270 and the references cited therein.
18. The reported procedure to prepare α-aminophosphonate under catalyst and solvent-free condition requires heating at 75-80 °C [B. C. Ranu and A. Hajra, Green *Chem*. 2002, 4, 551-554.
19. T. Mosmann, *J. Immunol. Meth.* 1983, **65**, 55-63.
20. Pyrimidine nucleoside aminophosphonate hybrids have been reported to be inactive against *L. donovani* [X. Zhang, Y. Qu, X. fan, C. Bores, D. Feng, G. Andrei, R. Snoeck, E. D. Clercq and P. M. Loiseau. *Nucleos. Nucleot. Nucleic Acids* 2010, **29**, 616-627.
21. (a) A. K. Chakraborti and R. Thilagavathi, *Bioorg. Med. Chem.* 2003, **11**, 3989-3996. (b) A. K. Chakraborti, B.

Gopalakrishnan, M. E. Sobhia and A. Malde, *Bioorg. Med. Chem. Lett.* 2003, **13**, 2473-2479. (c) A. K. Chakraborti, B. Gopalakrishnan, M. E. Sobhia and A. Malde, *Bioorg. Med. Chem. Lett.* 2003, **13**, 1403-1408. (d) For review please see L. Zhang, K. C. Tsai, L. Du, H. Li, M. Fang and W. Xu, *Curr. Med. Chem.* 2011**, 18**, 1-8.

22. SYBYL7.1, Tripos Associate Inc.; 1699, S. Hanley Rd., St.Louis, MO 631444, USA.
23. Z. Zhang, L. An, W. Hu and Y. Xiang, *J. Comput. Aided Mol. Des.* 2007**, 21**, 145-153.

Graphical Abstract

α-Aminophosphonates as novel anti-leishmanial chemotypes: synthesis, biological evaluation, and CoMFA studies

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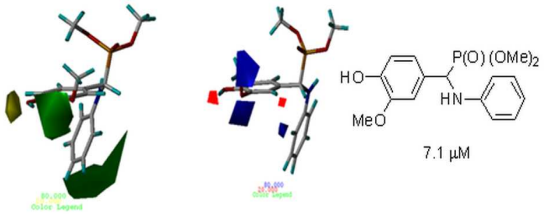

α-Aminophosphonates have been identified as novel antileishmanial chemotypes against *L. donovani* promastigote with low μM range activity.